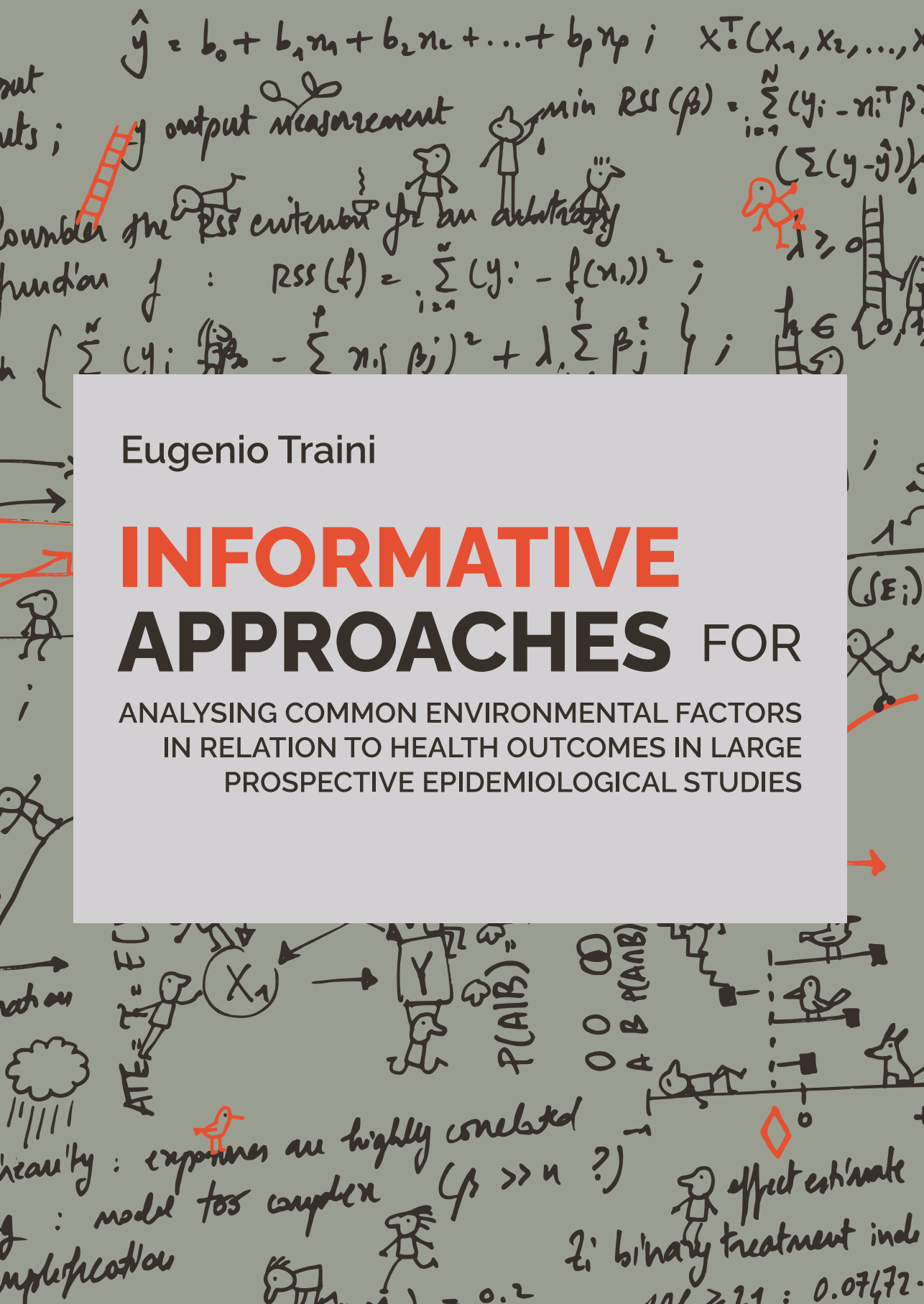

Eugenio Traini

INFORMATIVE APPROACHES FOR

ANALYSING COMMON ENVIRONMENTAL FACTORS IN RELATION TO HEALTH OUTCOMES IN LARGE PROSPECTIVE EPIDEMIOLOGICAL STUDIES

Informative approaches for analysing common environmental factors in relation to health outcomes in large prospective epidemiological studies

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Doctoral Thesis, Utrecht University

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Informative approaches for analysing common environmental factors in relation to health outcomes in large prospective epidemiological studies

Informatieve benaderingen voor de analyse van veelvoorkomende omgevingsfactoren in relatie tot gezondheidsuitkomsten in grootschalige prospectieve epidemiologische studies

(met een samenvatting in het Nederlands)

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Chapter 1: General Introduction

Ubiquitous exposures in the environment

The study of the impact of environmental stressors on human health is a subject of great interest within the scientific community, with significant implications for public health. This thesis considers various environmental factors that are commonly encountered in our everyday lives, with a specific emphasis on two exposure groups used as case studies across the different chapters: air pollution and radiofrequency electromagnetic fields (RF-EMFs).

Air pollution represents a large group of environmental exposures and a major contributor to the global burden of disease that affects millions of people worldwide (Cohen et al., 2017). Extensive research has been conducted over the years to quantify its adverse effects, with studies showing the harmful impact of air pollution on population health (Boogaard et al., 2022; Chen & Hoek, 2020). Along with population growth and the increase in urbanisation levels, several sources contribute to the increase in exposure levels, such as emissions from industries, pollution from vehicles, energy production processes, and construction activities. As a consequence, the regulation of air pollution, especially in urban areas, requires the implementation of different measures to control the levels of pollutants aiming at reducing the adverse health effects and bringing air quality to safe levels (The Economic Consequences of Outdoor Air Pollution | En | OECD, 2016).

Similarly to air pollution, exposure to RF-EMFs is ubiquitous in our society, and mobile phones and wireless communication devices represent major sources of exposure (van Wel et al., 2021). The increased use of mobile phones over
the past decades, along with the rapid spread of wireless technologies in the population, raised concerns about potential adverse health effects associated with the exposure to RF-EMFs. As a result, there is growing attention in studying the biological impact of RF-EMFs on health (Schüz et al., 2011; Verbeek et al., 2021).

Interestingly, despite the increase in frequency and duration of use of devices emitting radiofrequencies, the intensity of RF-EMF exposure among users has decelerated over time due to the advancement and evolution of new network generations, which involve higher efficiency of data transfer. As such, the exposure levels normally encountered in the population remain well below the established limits of safety for RF-EMF exposure (International Commission on Non-Ionizing Radiation Protection (ICNIRP), 2020; Iyare et al., 2021).

While nature and sources of air pollution and RF-EMF exposure differ significantly and are typically studied separately within the broader field of environmental epidemiology, they both share one crucial similarity: their widespread presence in the environment means that everyone is constantly exposed to them at varying levels.
Air pollution pervades urban and rural areas alike, affecting individuals indoors and outdoors, regardless of their location or lifestyle. Likewise, RF-EMFs permeate the modern built environment, with wireless communication devices omnipresent in society. As a consequence, even a slight increase or decrease in exposure levels of air pollution and RF-EMFs could potentially have significant implications on population health.
From a public health perspective, in addition to measured exposure levels, a relevant research stream within environmental epidemiology relates to how the exposure is perceived. In fact, by assessing exposure and risk perception, we complement information on measured and estimated exposure levels, ultimately providing important insights into health and well-being (Baliatsas et al., 2015; Cori et al., 2020).

Despite air pollution and RF-EMFs representing exposure groups of primary interest in epidemiological research, in the real world, individuals on a daily basis are exposed to a multitude of environmental factors, that have the potential to impact their health.
This research spans various environmental domains, which traditionally include exposures to chemicals, physical elements, and biological agents (Brunekreef, 2008; Pekkanen & Pearce, 2001). In addition to these determinants, to account for the complex interrelationship between environmental factors and individual behaviours, a considerable number of potentially modifiable risk factors have been incorporated, including diet, sedentary behavior, and other lifestyle factors and individual characteristics (Vineis et al., 2020). The totality of these factors contributing to establishing and preserving a healthy life throughout an individual's lifetime is commonly referred to as exposome (Vermeulen et al., 2020).
In this regard, the exposures comprising the component of the exposome (i.e. urban exposome) were considered in the thesis. Specifically, the urban exposome represents a rich data source where information on various aspects of the life of individuals, such as their physical activity, smoking and alcohol consumption, and other lifestyle factors, is included. Further information collected within the urban exposome involves chemical and physical exposures, such as the presence of chemicals and contaminants in water, in addition to air pollution and RF-EMFs, and neighbourhood characteristics, such as urban temperatures, presence of green and blue spaces, the access to healthy food options, healthcare facilities, and more (Ohanyan et al., 2022).

Health outcomes considered in the thesis

Multiple health outcomes are evaluated in the thesis based on their characteristics and distinctive methodological approaches used for their study: first, we consider head-

aches. Headache disorders, characterised by their diverse intensity and frequency, represent one of the most prevalent and incapacitating health conditions globally (GBD 2016 Headache Collaborators, 2018; Rasmussen et al., 1991; Steiner & World Headache Alliance, 2004). The etiology of headache appears to be complex and multifactorial, with both genetic and environmental factors playing a role (Robbins & Lipton, 2010; Svensson, 2004). Previous research emphasises the substantial impact of lifestyle and behavioural characteristics, as well as environmental factors such as air pollution and RF-EMFs, on the initiation and persistence of the symptoms. Therefore, it is possible that a combination of factors, rather than one single stressor, is responsible for the onset of headaches in the population (Friedman & De Ver Dye, 2009; Molarius et al., 2008; Ulrich et al., 2004).

The second outcome considered in the thesis is the condition known as electromagnetic hypersensitivity (EHS). EHS is a term used to define individuals who claim to be sensitive to EMFs (Dieudonné, 2020; Leszczynski, 2021). However, an important aspect of EHS is the concurrent attribution of health complaints to RF-EMFs, in which case the condition is more correctly specified as idiopathic environmental intolerance attributed to electromagnetic fields (IEI-RF).
In this thesis, for the sake of accuracy in terminology, we refer to IEI-RF to describe a set of self-reported non-specific symptoms that individuals attribute to electromagnetic field exposure, and EHS to describe individuals who claim to be sensitive but without necessarily attributing symptoms (Baliatsas et al., 2012; Martens et al., 2017; Röösli et al., 2004, 2010). For those subjects who claim to have IEI-RF, the condition shows a range of symptoms they believe are triggered or exacerbated by exposure to common sources of RF-EMFs, such as mobile phones, cordless phones, laptops, and other electronic devices emitting radiofrequencies. The reported symptoms vary widely, including headaches, fatigue, difficulty concentrating, sleep disturbances, and skin-related issues. In this regard, it is worth noting that clear diagnostic criteria for this condition are lacking (Stein & Udasin, 2020).

We considered mortality as an additional endpoint in the thesis. Mortality is a frequent study outcome in epidemiological studies as it represents the most serious endpoint. From a methodological perspective, it has the advantages of not displaying the transient nature typical of symptoms and being easily measured without ambiguity. Unlike headaches and EHS, mortality data is directly available from routinely collected sources such as death certificates and vital statistics registries.

Mechanisms of action

Understanding the mechanisms of action through which environmental exposures affect health is challenging, as these mechanisms often show traits of ambiguity and, as a

result, their interpretation is not straightforward. For some exposures, such as air pollution, the biological mechanisms of action are better defined than RF-EMF exposure.
In the case of air pollution, extensive research has revealed clear pathways involving oxidative stress, inflammation, and direct damage to cellular structures, which contribute to the onset of various health conditions, including respiratory and cardiovascular diseases, and neurological disorders, among others (Block & Calderón-Garcidueñas, 2009; Leikauf et al., 2020; Miller, 2020).

The scenario for RF-EMFs is more uncertain, particularly at the low exposure levels normally encountered in the population. On the one hand, a number of experimental studies have explored the effects of RF-EMF exposure on various outcomes, and the accepted biological mechanism from these studies to date is represented by tissue heating (D'Andrea et al., 2007). Furthermore, oxidative stress has been proposed as a potential biological response to RF-EMF exposure, though this remains controversial, especially since biological reactions at low exposure levels may be negligible in terms of health impact (Henschenmacher et al., 2022; Kamali et al., 2018; Tkalec et al., 2007). Conversely, observational studies are scarce and results inconsistent. Following results from the INTERPHONE study, which showed an isolated increased risk of glioma among mobile phone users classified in the highest decile of cumulative call-time (INTERPHONE Study Group, 2010), in 2011 the International Agency of Research on Cancer (IARC) classified RF-EMF exposure as possibly carcinogenic to humans (*IARC Publications Website - IARC Monographs on the Identification of Carcinogenic Hazards to Humans*, 2013). However, follow-up studies did not yield the same conclusion, and lack of association was also supported by recent findings from the international COSMOS and MOBI-Kids studies (Castaño-Vinyals et al., 2022; Feychting et al., 2024; Swerdlow et al., 2011).

If the potential mechanisms of action for low levels of RF-EMF exposure remain unclear for more established health outcomes, such as cancer, this uncertainty is possibly even more pronounced for outcomes that, due to their inherent nature and characteristics, appear to be transient in the population and therefore difficult to assess. This is the case for headache, which represents a highly prevalent condition in the population carrying a significant burden of disability.
In this respect, a number of experimental and epidemiological studies have investigated the role of RF-EMFs in the onset of headaches. Results from experimental studies focused on short-term exposure, and did not find strong evidence of an association (Augner et al., 2012; Cinel et al., 2008; Oftedal et al., 2007). Epidemiological studies investigating the health effects associated with long-term RF-EMF exposure showed varying results, such as the weak association between mobile phone use and migraine observed in a cohort study conducted in Denmark (Schüz et al., 2009), and the more recent findings from the cohort study conducted in Finland and Sweden suggesting that other factors

related to mobile phone use than RF-EMFs may explain the weak association that was found among users (Auvinen et al., 2019).

With regard to EHS and IEI-RF, the mechanisms of action remain uncertain (Baliatsas et al., 2009; Dieudonné, 2019; Stein & Udasin, 2020). Currently, three hypotheses can be identified (Dieudonné, 2020): first, the biological route assumes a direct effect of RF-EMF exposure on reporting symptoms. The second route, which reflects the cognitive hypothesis, argues that perceived exposure and risk promote a nocebo response that generates symptoms. The third route, in accordance to the attributive hypothesis, argues that symptoms may be attributed by an individual to RF-EMF exposure to help explain a health problem for which no diagnosis has been made.

Challenges in studying how environmental factors influence human health

Well-formulated research questions and hypotheses serve as pillars to efficiently design an epidemiological study, ensure reliable inferences, and draw meaningful conclusions from the analysis (Kleinbaum et al., 2013). However, researchers in environmental health encounter several challenges of different nature when analysing epidemiological data. Addressing these challenges necessitates appropriate statistical techniques, and, at times, novel approaches to better understand the underlying causes of action in order to prevent health effects.

Here, some of these challenges are briefly outlined: first, depending on the exposure being considered, understanding the underlying potential mechanisms linking exposures to health outcomes may not be straightforward. This difficulty is relatively common in studies assessing the health effects of non-ionising radiation, where the biological mechanisms of action at the exposure levels generally encountered in the population are uncertain (Erwin, 1988; Stein & Udasin, 2020). However, for exposures where the mechanisms of action are clearer, such as in the case of air pollution, the high correlation structure existing between the air pollutants introduces further complexity in the analysis and interpretation of the results, making it difficult to disentangle the underlying mechanisms in the exposure-outcome association (Billionnet et al., 2012). This can also be the case for devices emitting RF-EMFs, where the exposure could correlate with user behaviours, and therefore the underlying mechanisms of action may not be easily distinguishable (Schoeni et al., 2017). In this scenario, the main challenge lies in discerning RF-EMFs from other aspects of mobile phone use, such as those reflecting the behaviour of the user, which may not necessarily result in high exposure levels (e.g. texting) (van Wel et al., 2021).
Second, in situations where researchers aim to investigate the occurrence of chronic conditions or symptoms, which inherently undergo changes over time due to their nature, relying on a single follow-up may not provide sufficient insights into the potential

patterns involved in the exposure-outcome association, and common statistical methods may struggle to unravel the underlying dynamics of change (Kowall et al., 2012; Martens et al., 2018).
An example is provided by EHS, for which previous studies indicated a frequent turnover in individuals reporting symptoms over time, suggesting that EHS is transient and highly temporary in the population (Kowall et al., 2012; Martens et al., 2018; Röösli et al., 2010). In these situations, additional complexity may arise from the characteristics of the exposure itself, such as in the case of RF-EMF exposure that is subject to frequent changes over time. In addition, the risk of reverse causation, which could potentially lead to misinterpretation of the findings, is common in these scenarios.
Third, in settings where the aim is to evaluate the effect of multiple exposures of interest occurring simultaneously, such as in the case of environmental mixtures, regression techniques may fail to capture underlying signals in the mixture-outcome association, including interactions and synergistic effects. In these scenarios, better-suited approaches should be considered (Agier et al., 2016; Barrera-Gómez et al., 2017).

With regard to environmental mixtures, some of the most common research questions that researchers may want to answer include addressing the high correlation structure usually present among the components of the mixture, as well as the presence of interactions and nonlinearities, the estimation of the overall effect of the mixture and the identification of the main contributors within the mixture responsible for the effect, the integration of environmental mixtures in mediation analysis, and more (Maitre et al., 2022; Bellavia et al., 2021; Wilson et al., 2018; Blum et al., 2020; Bellavia et al., 2019). In this regard, within the causal inference framework, particular attention has been directed over the past few years towards the development of novel approaches aimed at estimating causal effects and establishing causal relationships in epidemiological studies (Wager & Athey, 2018; Williams & Crespi, 2020).

Following this brief overview of some of the challenges commonly encountered in the analysis of prospective data in environmental epidemiology, that is by no means intended to be exhaustive, I introduce in this thesis some novel approaches designed to tackle different challenges across scenarios of varying complexities with the underlying aim to determine the most plausible mechanisms of action and elucidate what may, or may not, be causally related.

Aim of the thesis

The overarching aim of the thesis is to propose informative approaches for the analysis of common environmental factors in relation to health outcomes, across different scenarios, using data from large prospective epidemiological studies. These approaches aim to provide valuable insights and understanding of exposure-outcome associations, in-

cluding mechanisms of action and potential causal pathways, in order to prevent health effects.

This thesis has the following specific aims:

i. To extract meaningful insights and draw conclusions regarding exposure-outcome associations in scenarios where the mechanisms of action are uncertain and/or difficult to determine, by exploring different potential pathways while optimising available exposure data;
ii. To explore the temporal dynamics of health outcomes characterised by considerable fluctuations over time, by analysing data across multiple time points, accounting for time-dependent risk factors;
iii. To explore an environmental mixture and determine the causal effect of its components on health, within a simplified exposure-outcome scenario involving a preselected set of exposures and mortality as endpoint;
iv. To identify a relevant set of exposures and estimate their causal effects in studies assessing the impact of multiple exposures occurring simultaneously on health, in an exposure-outcome scenario characterised by high-dimensional exposure data typical of exposome-wide studies.

Study design and databases used in the thesis

In this thesis, data from large prospective epidemiological studies are analysed. Cohort studies represent one of the most commonly used study designs for the analysis of observational data in environmental epidemiology. Within this framework, the conduct of prospective studies plays a crucial role in exploring the relationship between exposures and health outcomes. Their distinctive characteristic is the temporal sequence, where the exposure is assessed before the outcome occurs, allowing for the evaluation of the relationship over time (Morgenstern & Thomas, 1993). As a result, using a prospective study design may facilitate the identification of potential causal relationships, although this characteristic is not sufficient to prove causality (Nowinski et al., 2022).

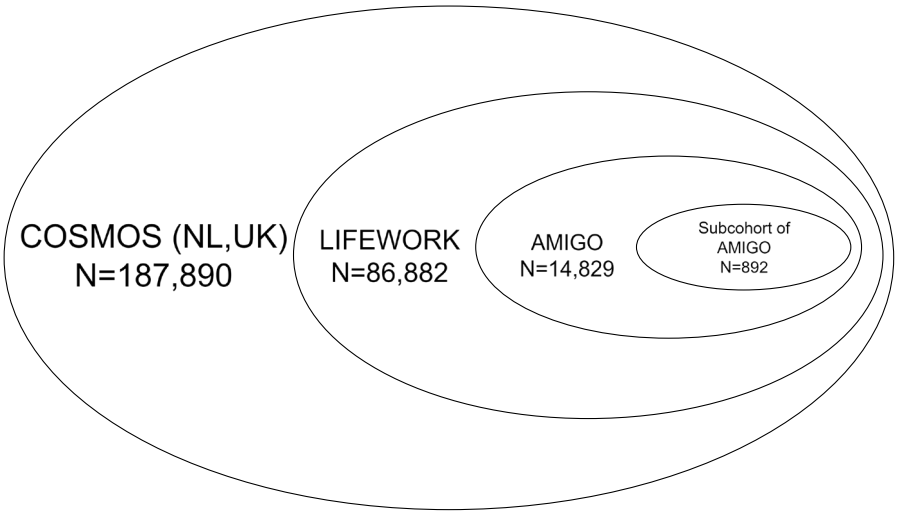
To achieve the objectives of the thesis, data from the cohort study of mobile phone use and health (COSMOS), LIFEWORK, and the Dutch occupational and environmental health cohort study (AMIGO) were analysed (Figure 1).
COSMOS is an international study investigating possible health effects of long-term use of mobile phones and other wireless technologies (Schüz et al., 2011). The specific objective of COSMOS is to track the health of over 250,000 individuals over a long period of time to determine whether adverse health effects are observed in relation to their use of mobile phones and other wireless technologies. Information is obtained from repeated harmonised questionnaires, repeated downloads from traffic operators, and health registries depending on data availability. COSMOS is an international consortium

involving Denmark, Finland, Sweden, the Netherlands, the UK, and France. It was initiated between 2008 and 2012 in all countries except France, which joined in 2019. All countries, expect France, completed the first follow-up by 2017. According to the COSMOS protocol, data from participating countries are pooled to achieve sufficient statistical power for investigating mobile phone use in relation to several health outcomes, including brain cancer, headaches, and neurological disorders. A significant strength of COSMOS lies in its prospective design, which minimises recall and selection biases. In this thesis, data from the Netherlands and the UK cohorts of COSMOS were analysed.

LIFEWORK is a large federated prospective cohort in the Netherlands that quantifies the health effects of occupational and environmental exposures (Reedijk et al., 2018). With nearly 90,000 participants, LIFEWORK represents the second largest contributor to the international COSMOS study. In 2011, the nationwide prospective cohort LIFEWORK was initiated to explore occupational and environmental health factors among people living in the Netherlands. Representing the Dutch contribution to COSMOS, LIFEWORK specifically focuses on assessing EMF exposure from mobile phones and other wireless devices. Three Dutch cohorts, namely EPIC-NL, Nightingale, and AMIGO, are part of LIFEWORK and participants completed the first follow-up questionnaire between 2015 and 2017.

AMIGO is the Dutch occupational and environmental health cohort study and represents one of the subcohorts included in LIFEWORK, which investigates occupational and environmental determinants of diseases and well-being relying on a multidisciplinary and life course approach (Slottje et al., 2014). In AMIGO, approximately 14,000 individuals were recruited in the Netherlands between 2011 and 2012, to explore underlying causes of health conditions in the population, such as respiratory diseases, cardiovascular diseases, and dementia, and uncover the potential influence of the daily living environment on well-being. A subcohort of AMIGO was established in 2013, and a follow-up questionnaire was completed by this subgroup of participants in 2021, with dedicated questions to assess relationships between exposure, risk perception, symptom reporting and symptom attribution to environmental factors, including RF-EMFs.

Figure 1. Overview of the data used in the thesis.



Outline of the thesis

In this section, I provide an overview of the content covered in the different chapters of the thesis, outlining their main objectives and the methodological approaches used.

In Chapter 2, we conducted a prospective analysis of the association between mobile phone use and the occurrence of headaches analysing pooled data from the Netherlands and the United Kingdom as part of the COSMOS project. Given that the potential mechanisms of action linking mobile phone use and headaches are uncertain, we explored two possible causal pathways: RF-EMF exposure and the behavioural aspect of mobile phone usage with negligible RF-EMF exposure. By optimising the exposure data available in COSMOS, we were able to disentangle the exposure-outcome relationship, ultimately identifying the most plausible route for this association.

In Chapter 3, we explored the temporal dynamics of attributing symptoms to RF-EMFs (IEI-RF) by assessing factors related to developing, maintaining, or discarding IEI-RF over 10 years, using data from the subcohort of AMIGO. We modelled the process in which participants move through a series of states of IEI-RF by estimating multi-state Markov models, a flexible statistical technique for estimating rates of transition between stages or health conditions. Finally, we applied logistic regression to explore predictors of sensitivity at follow-up, without necessarily attributing symptoms (EHS).

In Chapter 4, we proposed a pluralistic approach to prospectively explore the relationship between a mixture of air pollutants and mortality in LIFEWORK. Using targeted methods

for high-dimensional exposures, we assessed the relevance of mixture's components in the mixture-outcome association, and investigated interactions and nonlinearities. Based on these results, we built a multivariate generalised propensity score model to jointly estimate the causal effects of the pollutants on overall mortality.

In Chapter 5, we prospectively explored the urban exposome of AMIGO in relation to headaches by using a combination of machine learning techniques. Specifically, we followed a two-stage approach where we first applied Boruta to identify relevant exposures in the exposome-outcome association, and then estimated causal forest to quantify the causal effect of these exposures on the occurrence of headache.

In Chapter 6, the main findings of this thesis are summarised, followed by discussions of the different approaches used, including challenges and limitations associated with their use, and policy implications and possible directions for future research.

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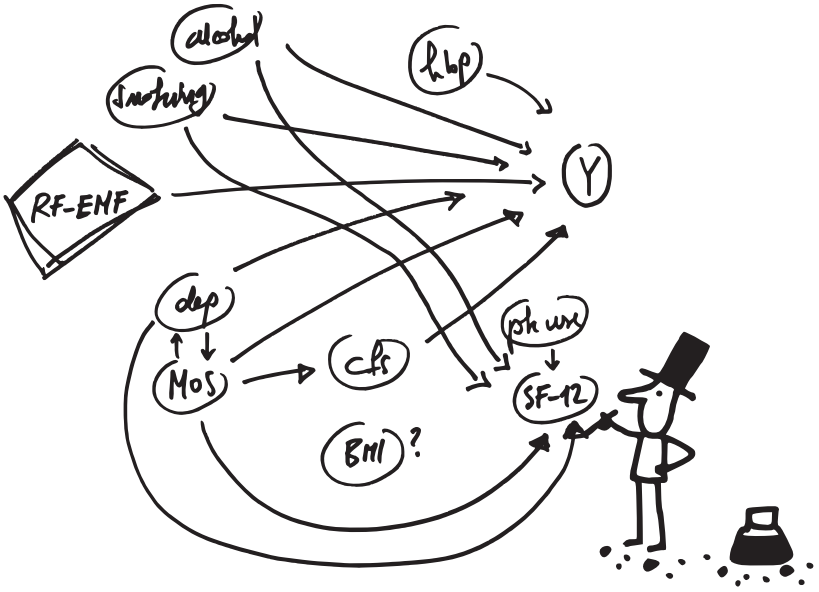
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Chapter 2: Headache in the international Cohort Study of Mobile Phone Use and Health (COSMOS) in the Netherlands and the United Kingdom

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Abstract

Headache is a common condition with a substantial burden of disease worldwide. Concerns have been raised over the potential impact of long-term mobile phone use on headache due to radiofrequency electromagnetic fields (RF-EMFs). We explored prospectively the association between mobile phone use at baseline (2009-2012) and headache at follow-up (2015-2018) by analysing pooled data consisting of the Dutch and UK cohorts of the Cohort Study of Mobile Phone Use and Health (COSMOS) (N=78,437). Frequency of headache, migraine, and information on mobile phone use, including use of hands-free devices and frequency of texting, were self-reported. We collected objective operator data to obtain regression calibrated estimates of voice call duration. In the model mutually adjusted for call-time and text messaging, participants in the high category of call-time showed an adjusted odds ratio (OR) of 1.04 (95% CI: 0.94–1.15), with no clear trend of reporting headache with increasing call-time. However, we found an increased risk of weekly headache (OR=1.40, 95% CI: 1.25–1.56) in the high category of text messaging, with a clear increase in reporting headache with increasing texting. Due to the negligible exposure to RF-EMFs from texting, our results suggest that mechanisms other than RF-EMFs are responsible for the increased risk of headache that we found among mobile phone users.

Introduction

Over the past few decades, wireless technology has rapidly proliferated throughout society, revolutionising how we interact worldwide. As a result, frequency and duration of use of wireless devices have increased over time, while the intensity of exposure to radiofrequency electromagnetic fields (RF-EMFs) has seen a reduction following the progression and evolution of new network generations (Iyare et al., 2021). With the expanding uptake of wireless devices and the advancements in mobile technologies, concerns regarding the potential health consequences of long-term exposure to RF-EMFs have been raised. Several experimental and epidemiological cross-sectional and case-control studies have explored the possible link between RF-EMF exposure and symptoms such as headache and migraine. Results showed no consistent evidence of adverse health effects at the exposure levels typically encountered in the population (Augner et al., 2012; Cerutti et al., 2016; Cinel et al., 2008; Durusoy et al., 2017; Oftedal et al., 2007; Wang et al., 2017). However, results from cohort studies are still scarce.

The Cohort Study of Mobile Phone Use and Health (COSMOS) is a large prospective cohort study of mobile phone users comprising more than 300,000 adults who will be followed up for over 25 years. COSMOS was established in six European countries (Denmark, Finland, France, Sweden, the Netherlands, and the United Kingdom (UK)) to prospectively investigate possible health effects associated with long-term use of mobile phones and other wireless technologies (Schüz et al., 2011). Several health outcomes are being investigated, including headache and migraine. These represent important causes of disability worldwide with a high public health relevance (GBD 2016 Headache Collaborators, 2018), and the possible association with RF-EMF exposure among mobile phone users has yet to be clarified.

A study conducted in Sweden and Finland as part of COSMOS found limited evidence for an association between weekly headache and the highest level of mobile phone use and no clear trend with increasing call-time (Auvinen et al., 2019). The association of headache with call-time appeared stronger for calls via the Universal Mobile Telecommunication System (UMTS) (3G) network than via the older Global System for Mobile (GSM) (2G) telecommunications technology, despite the latter involving higher RF-EMF exposure levels to the head (van Wel et al., 2021).

In this study, we assessed the relationship between mobile phone use at baseline and headache at follow-up by exploring two mobile phone use activities: voice calling and texting. Calling, depending on the technology and other usage characteristics, such as the position of the device relative to the body and the use of hands-free devices, exposes the head to different levels of RF-EMFs. Texting produces negligible RF-EMF exposure. Therefore, any association is hypothesized to have other underlying mechanisms than RF-EMF exposure.

Methods

Study participants

In this prospective study, we pooled data from the Dutch and UK cohorts of COSMOS comprising more than 180,000 participants who completed the baseline questionnaire providing information on mobile phone use, health, environmental exposures, lifestyle, and demographics.

In the Netherlands, 88,466 participants were enrolled in three cohort studies between 2011 and 2012, constituting the LIFEWORK cohort, representing the Dutch contribution to COSMOS. LIFEWORK was designed as a federated study integrating the Nightingale Study, the Occupational and Environmental Health Cohort Study (AMIGO), and the European Prospective Investigation into Cancer and Nutrition in the Netherlands (EPIC-NL). In LIFEWORK, a follow-up questionnaire was completed between 2015 and 2017 by 53,697 participants. Compared to the general adult population in the Netherlands, there is a higher proportion of women (89.2%) and the average age is older (around 50 years old). The rationale, study design, and participant recruitment in LIFEWORK were discussed in detail elsewhere (Beulens et al., 2010; Pijpe et al., 2014; Reedijk et al., 2018; Slottje et al., 2014).

In the UK, 99,424 participants were recruited from across the country between 2009 and 2012 and filled in the baseline questionnaire. Recruitment was from mobile phone subscriber lists (65%) and the UK edited electoral register (35%). A follow-up questionnaire was completed by 45,308 UK participants between 2015 and 2018. UK COSMOS participants seem to enjoy better health than the general adult population in the UK, as evidenced by a lower current smoking rate and lower prevalence of obesity. The rationale, study design, and participant recruitment of UK COSMOS were discussed in detail elsewhere (Toledano et al., 2017).

After exclusions, the pooled cohort of Dutch and UK participants with baseline and follow-up data consisted of 78,437 individuals (Figure 1).

Exposure assessment

In this study, the exposure information was collected prospectively in relation to the health outcome being analysed. Participants self-reported information on their mobile phone use for the 3 months before baseline, via questionnaire. This included weekly call-time, the proportion of use with hands-free devices, frequency of text messages, use of multiple mobile phones, and whether other people used the participants' mobile phone(s). Call-time on cordless phones was also reported.

In addition to self-reported mobile phone use, outgoing and incoming voice call durations were obtained during the same 3-month period at baseline from network operators for participants (with consent) who had a subscription under their own name. The proportion of participants for whom complete data from network operators at baseline

was available was 3% (the Netherlands) and 58% (the UK). Information on 2G and 3G networks, technologies that were in use at the time of this study, was not available for these two cohorts.

Self-reported duration of voice calling on a mobile phone is considered an error-prone proxy for mobile phone use (Aydin et al., 2011; Berg et al., 2005; Heinävaara et al., 2011; Vrijheid et al., 2009). We leveraged self-reported and objective operator-recorded mobile phone use data available in the subset of participants with complete network operator data to deal with measurement error in self-reported mobile phone data and improve the estimation of exposure-outcome relationships in COSMOS. Country-specific regression-calibrated estimates based on operator data for both incoming and outgoing mobile phone calls (the average operator-recorded value per category per country) were applied to self-reported weekly mobile phone call-time categories, for all participants (Reedijk et al., 2023).

We adjusted call-time according to the proportion of hands-free use the participant reported (response options "hardly ever", "less than half of the time", "about half of the time", "more than half of the time", "always or nearly always"), reducing voice call duration by 5%, 10%, 25%, 35%, and 50%, respectively, for each hands-free use category (Goedhart et al., 2015).

To assess the potential effects of RF-EMF exposure on headache accounting for co-exposure from multiple sources, we estimated the RF-EMF dose to the brain using an organ-specific integrated exposure model (IEM). The IEM uses specific absorption rate transfer algorithms to provide RF-EMF weekly dose estimates (mJ/kg/week) using source-specific attributes (e.g. output power, distance), personal characteristics (e.g. height and weight) and usage patterns. Exposure input data for the IEM included call-time on mobile phones and cordless phones as these were identified as primary contributors to the brain dose (van Wel et al., 2021).

Finally, call-time and RF-EMF dose exposure metrics were categorised into four exposure categories ("very low", "low", "medium", and "high") based on the pooled exposure distribution, with cut-offs aligned as close as possible to predefined percentiles ("lowest 30%", "30th–69th percentile", "70th–89th percentile", "90th–100th percentile") (Supplementary Table 1). "Low" was selected as the referent exposure category in regression models as it had the highest proportion of both Dutch and UK participants.

The number of text messages sent on a mobile phone at baseline was used as a proxy for use with negligible RF-EMF exposure. It was categorised into three exposure categories ("low", "medium", and "high") corresponding to the response options "never/less than 1 text message per week/1–6 text messages per week", "1–9 text messages per day", "10–29 text messages per day/30 or more text messages per day". For clarity, text messages here refer to Short Message Service (SMS) via the mobile cellular network, and does not include instant messaging via the internet. An overview of the exposure metrics used in

this study is provided in Supplementary Table 2.

Headaches and migraine

Headaches were self-reported at baseline and follow-up. The primary outcome was weekly headache at follow-up. The secondary outcomes were severe weekly headache, daily headache, and migraine diagnosis at follow-up. Headaches were defined according to the question "How often do you get headache at the moment?", with response categories of "almost every day", "5 or 6 days a week", "3–4 days a week", "once or twice a week" "1–2 days per month", and "less often". The Headache Impact Test (HIT-6) score with a cut-off of 56 points defined severe weekly headache. The HIT-6 is a tool used to measure the impact headaches have on one's ability to function in various aspects of daily life, including work, school, home, and social contexts. The score, ranging from 36 to 78 points, provides a measure of the degree to which headaches affect daily life and functioning, with higher scores indicating a more significant impact on the participant's overall life (Kosinski et al., 2003). Migraine diagnosis at follow-up was defined based on the question "Have you ever been diagnosed by a medical doctor with migraine?". To avoid potential reverse causation, we restricted all analyses to participants who did not report weekly or more frequent headaches at baseline (N=66,858) and likewise for migraine diagnosis (N=53,576) (Auvinen et al., 2019).

Covariates

We identified the following potential confounders of the associations between mobile phone use and headaches a priori based on previous studies (Auvinen et al., 2019; Farashi et al., 2022; Wang et al., 2017): sex, age group (18-29, 30-39, 40-49, 50-59, 60+), country (the Netherlands, the UK), highest level of education attained (elementary, secondary and higher), body mass index (BMI) group (normal or underweight, overweight or obese), general health indicator (good, poor), sleep disturbance index, painkiller use (yes, no), depression diagnosis (yes, no), high blood pressure diagnosis (yes, no), smoking status (never, former, current), alcohol consumption (never, former, current). Models were adjusted for these factors, as measured at baseline, a priori.

Statistical analysis

Missing values were imputed on covariates only through multivariate imputation by chained equations (complete-case data set including 58,229 participants), performed separately for each cohort. All covariates (except country), exposures, and study outcomes were used as predictors, and Rubin's rule was used to combine the regression parameters over 30 imputed data sets (Buuren & Groothuis-Oudshoorn, 2011; White et al., 2011).

Descriptive statistics of the study population were calculated overall, by country, and by exposure level. Correlation between exposure metrics was evaluated using Spearman's

rank correlation coefficients.

To evaluate the exposure-outcome associations, we estimated multivariable logistic regression models. We first assessed call-time and texting exposures separately, and then mutually adjusted for both exposures in one model. Weekly minutes of call-time at baseline (country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) was the primary exposure metric.

We calculated a p-value for linear trend across exposure categories as an ordered factor, to test for dose-response relationships between exposure and outcome.

We performed stratified analyses for sex, age group, and country. To examine interactions between call-time and texting and potential modifiers (sex, age group, and country) on the risk of weekly headache, we tested for significance of interaction terms added to the models using a likelihood ratio test.

As secondary analyses, we analysed self-reported mobile phone call-time adjusted by the proportion of hands-free use (SR-hfa), operator-recorded call-time adjusted by the proportion of hands-free use (OP-hfa), and the RF-EMF estimated dose to the brain with the IEM ($IEM_{RC\text{-}hfa,\ DECT}$) as exposure metrics at baseline, respectively.

We performed the following sensitivity analyses: first, we used country-specific regression calibrated call-time estimates without adjustment for hands-free use (RC) as the exposure metric. Second, we excluded painkiller use as a model covariate, in case use results from headaches. Third, we lowered the cut-off for the "high" exposure category to approximate the 80th percentile of the pooled exposure distribution - for comparison with the main analyses in which the top 10th percentile was used to define highly exposed participants. Fourth, we replicated the analyses by categorising the RC-hfa exposure into quartiles for comparison with the main findings. Last, we performed a complete-case analysis to compare with results obtained on imputed datasets.

All analyses were performed using R Statistical Software (v4.2.3; R Core Team 2023) (*R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. URL Https://Www.R-Project.Org/.*, n.d.). Computing code for all analyses presented is available on request.

Results

Baseline characteristics of the study population by categories of call-time and texting are presented in Table 1 and Supplementary Table 3 (baseline characteristics by country in Supplementary Tables 4-7), respectively. No relevant differences in the distribution of baseline characteristics of the study participants were observed when including those who did not complete a follow-up questionnaire (Supplementary Tables 8-9). There was a greater proportion of women than men across all levels of exposures, as almost 90% of the Dutch cohort were women. Individuals in the high call-time (RC-hfa) category were all UK participants. The baseline distribution of RC-hfa was skewed towards low values, with Dutch participants on average reporting less call-time than the UK participants (Fig-

ure 2).

Call-time exposure metrics were strongly correlated with the RF-EMF estimated dose (Spearman's correlation coefficient ρ: $0.63 \leq \rho \leq 0.99$). We observed weak to moderate correlations between texting and call-time metrics and RF-EMF estimated dose (Spearman's correlation coefficient ρ: $0.24 \leq \rho \leq 0.54$) (Figure 3).

Of 66,858 participants who were free of weekly headache at baseline and included in analysis of call-time and texting, 5,452 (8.2%) reported weekly headache at follow-up, and 382 (0.6%) reported daily headache. 1,660 (2.5%) individuals were classified as having severe weekly headache out of 66,234 with complete information on the HIT-6 score at follow-up. Of 53,576 participants free of migraine at baseline, 1,812 (3.4%) reported migraine at follow-up.

In adjusted single exposure models, we found an increased risk of weekly headache at follow-up (OR=1.10, 95% CI: 1.01–1.22) in the high category of regression calibrated call-time at baseline (RC-hfa), with a clear increase of reporting headache with increasing call-time (P trend=0.002) (Table 2).

Similarly, we found an increased risk in weekly headache at follow-up (OR=1.42, 95% CI: 1.28–1.58) in the high category of texting, also with a clear trend of increasing risk with increasing texting (P trend<0.001) (Table 3).

Results from two-exposure models mutually adjusting for both call-time and texting at baseline, showed substantially lower risk estimates for weekly headache in the high call-time (RC-hfa) category (OR=1.04, 95% CI: 0.94–1.15), and no evidence of a trend (P trend=0.292) (Table 2). Associations with texting were robust to adjustment for call-time: we observed an increased risk of weekly headache in the high category of texting (OR=1.40, 95% CI: 1.25–1.56) and a trend of increasing risk with increasing texting frequency (P trend<0.001), in line with results from the single-exposure model (Table 3).

Regarding secondary health outcomes, we found consistent patterns of results for severe weekly headache and migraine at follow-up in terms of increased risk estimates and significant trends. Increasing risk of daily headache was associated with increasing texting (P trend<0.001) but not with increasing call-time (P trend=0.448) (Tables 2–3).

We did not detect interactions between call-time and texting, respectively, and potential modifiers (sex, age group, and country) on the risk of weekly headache, and results showed that the exposure-response associations were remarkably consistent across sex, age groups and countries, particularly with regard to texting (Supplementary Tables 10–11).

Secondary analyses, including self-reported mobile phone call-time and operator-recorded call-time as exposure metrics in the separate regression models produced compatible results with the main analysis of regression calibrated call-time (Supplementary Tables 12–15). Results using the RF-EMF estimated brain dose as exposure metric in the models were consistent with those using regression calibrated call-time (Supplemen-

tary Tables 16–17). The models using the hands-free unadjusted regression calibrated call-time exposure metric showed no further increase in risk among users compared to the main analyses (Supplementary Tables 18-19). Results from sensitivity analyses were compatible with the main findings (Supplementary Tables 20–29).

Discussion

In this large international prospective cohort of mobile phone users in the Netherlands and the UK, mobile phone use for calling and texting at baseline was associated with headaches at follow-up. Mutually adjusting for both call-time and texting considerably attenuated risk estimates for call-time, while associations with texting were still strong and robust to adjustment, with a clear exposure-outcome gradient.

Headache has been linked to excessive mobile phone use, but the mechanism by which mobile phone use may cause symptoms is not properly understood (Cerutti et al., 2016; Frey, 1998; Hocking, 1998; Oftedal et al., 2000; Schoeni et al., 2015; Wang et al., 2017). Previous research in adolescents has suggested that other exposures related to mobile phone use, but not exposure to RF-EMFs, should be considered the causal factor for various symptoms, as the strongest associations were found with activities that cause minimal RF-EMF exposure to the head, such as texting or gaming (Schoeni et al., 2017). Other studies have indicated that stress or unfavourable usage, such as late-night use, may be associated with an increase in reported health symptoms, such as headache (Röösli, 2008; Szyjkowska et al., 2014; Thomée et al., 2011). It is therefore crucial to distinguish between using a mobile phone for calling and other activities that expose the brain to RF-EMFs at lower levels, such as Internet browsing (Cabré-Riera et al., 2022a; SSM's Scientific Council on Electromagnetic Fields, 2020).

Our study attempted to disentangle the exposure-outcome gradient by considering call-time as a proxy for RF-EMF exposure and texting as a proxy for usage with negligible RF-EMF exposure to the brain (Wall et al., 2019). This study's mobile phone usage data was gathered between 2009 and 2012. During those years, texting was the most popular activity unrelated to RF-EMF exposure.

In both scenarios, we found an increased risk of headache in the high exposure category of mobile phone use with a positive exposure-outcome gradient confirmed by the test for trend. The attenuated risk estimates for call-time in the mutually adjusted model argue against an effect of exposure to RF-EMFs due to the negligible exposure attributed to texting. This conclusion is also supported by comparing call-time analyses with and without hands-free adjustment, where no risk reduction was found among users for the adjusted exposure metrics.

In this study, the distribution of the exposure, specifically regarding call-time, differed between Dutch and UK participants. Mobile phone usage behaviour across countries cannot be assumed to be identical due to various factors such as cultural, economic, technological, and market dynamics (Böhm, 2015). To assess the consistency of our find-

ings, we showed that defining the top exposure category for call-time based on the 80th percentile cut-off, thereby ensuring the inclusion of Dutch participants in the "high" exposure category, yielded results consistent with those obtained using the 90th percentile as a cut-off. These findings suggested that the association we found between call-time and headache was driven not only by UK but also Dutch participants. Of note, all analyses were adjusted for country of residence.

Our study has several strengths. This is the largest prospective study to explore the relationship between mobile phone use and headache using a prospective study design and several exposure metrics, including the regression calibrated estimates where operator-recorded and self-reported call-time were combined to improve the estimation of the exposure by reducing recall bias resulting in more informative exposure-outcome relations (Reedijk et al., 2023).

Furthermore, the RF-EMF estimated dose to the participant's brain calculated with the IEM provided detailed estimates of exposure levels by considering multiple sources of exposure and the intensity of RF-EMFs associated with specific functions (such as the specific absorption rate) (van Wel et al., 2021).

An accurate exposure assessment of RF-EMFs from the use of mobile phones has proved difficult as the dose of exposure depends on several factors, which include source-specific attributes (output power), characteristics of the subject (age, sex, body mass), and the way devices are used (position relative to the body, type of use, duration of use) (Lönn et al., 2004; van Wel et al., 2021). Nevertheless, the quantity and quality of data collected in COSMOS allowed us to characterise mobile phone use for calling and texting in detail. Given the speed at which technology is developing and the need to assess RF-EMF exposure more thoroughly, we used the IEM to estimate the integrative RF-EMF dose to the brain of participants. The IEM represents the most complete RF-EMF dose estimation tool to date. It can estimate RF-EMF dose to different anatomical sites, including the brain as target organ for headache (Cabré-Riera et al., 2022b; van Wel et al., 2021).

Our study also has limitations. First, we did not have information about "true" RF-EMF exposure. Exposure to RF-EMFs emitted by wireless devices is difficult to quantify, particularly in large populations and over extended periods, as it depends on different factors, such as reception quality or other factors influencing signal strength. In our study, we calculated several exposure metrics as proxies for RF-EMF exposure, which allowed us to estimate the average individual RF-EMF exposure in the population. Additionally, information on other aspects of usage, such as screen time, blue light exposure or unfavourable use at night, may be helpful to include in future studies.

For highly transient and acute symptoms such as headache, using the peak of RF-EMF exposure might be theoretically preferable over the weekly exposure assessed in our study. However, adopting this approach would require substantially different exposure assessment methods that are impractical for large cohort studies, such as asking partici-

pants to regularly fill in a detailed usage diary. Given the study design and methodology used to assess RF-EMF exposure in COSMOS, the analysis of the association between RF-EMF peak exposure and reporting of headache symptoms was precluded. In light of the transient nature of headaches, future research may explore the potential effect of peak RF-EMF exposure on symptom onset more thoroughly.

The composition of the Dutch cohort is not representative of the adult population of the Netherlands with respect to sex and age. In fact, the majority of participants in LIFEWORK were over the age of 50 years and the Nightingale study source population comprised women who were registered as having completed training to be a nurse in the nationwide register for healthcare professionals in the Netherlands. Furthermore, the EPIC study source population was based on women participating in a regional breast cancer screening program (Reedijk et al., 2018). We, a priori, had no indications that the effects of RF-EMFs on the occurrence of headaches would be different between men and women, or across age groups. In any case, these characteristics in the study population are unlikely to have hampered the ability to detect and estimate exposure–outcome associations, given the adequate control of confounding variables that were included in our analyses.

Finally, participants reported headache at baseline and follow-up, and no information was available in between. Therefore, these evaluations might not accurately reflect symptoms between these two time points, particularly for a transient condition such as headache. However, secondary analyses on migraine diagnosis, which should be less likely to change over time, were conducted, and results were consistent with those on headaches.

According to the Global Burden of Disease study, headaches are among the most common nervous system disorders, with migraine being the second among the world's causes of disability (Steiner et al., 2020; Stovner et al., 2022). These conditions are identified as a major public health concern, given the deleterious impact on the personal pain burden, the resulting impairment in the quality of life of those affected, and the related societal costs (Stovner et al., 2006).

Our results showed that the associations with headache and migraine found with call-time were largely explained by texting, and this suggests that the mechanism may be related to lifestyle, other exposures, or behavioural factors associated with the usage of mobile devices. Given the ubiquity of mobile phone use worldwide, more research is warranted to understand the exact underlying mechanism generating headaches and migraines among mobile phone users to develop options for prevention. Future research should also encompass the rapid technological advances and changes in mobile phone usage habits among the population and the associated possible health consequences.

Conclusions

In summary, we found that the use of mobile phones, particularly texting, is associat-

ed with headaches and migraines, and the associations with call-time were largely explained by texting. As the associations are driven more by text messaging than call-time, they do not appear to be explained by RF-EMF exposure from the mobile device but are likely to reflect lifestyle, other exposures, or behavioural factors associated with mobile phone use.

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Table 1. Characteristics of the participants by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)).

	Amount of mobile phone use at baseline (call-time in categories[a])				
	Very low (N=23211)	**Low (N=31310)**	**Medium (N=14475)**	**High (N=9441)**	**Overall (N=78437)**
Sex, n (%)					
Men	3420 (14.7)	7648 (24.4)	5665 (39.1)	4344 (46.0)	21077 (26.9)
Wormen	19791 (85.3)	23662 (75.6)	8810 (60.9)	5097 (54.0)	57360 (73.1)
Age group (years), n (%)					
18-29	578 (2.5)	2750 (8.8)	1703 (11.8)	1582 (16.8)	6613 (8.4)
30-39	1868 (8.0)	4305 (13.7)	2293 (15.8)	1719 (18.2)	10185 (13.0)
40-49	5103 (22.0)	6982 (22.3)	2838 (19.6)	1813 (19.2)	16736 (21.3)
50-59	7108 (30.6)	10322 (33.0)	4820 (33.3)	2802 (29.7)	25052 (31.9)
60+	8554 (36.9)	6951 (22.2)	2821 (19.5)	1525 (16.2)	19851 (25.3)
Country, n (%)					
The Netherlands	19462 (83.8)	20401 (65.2)	4780 (33.0)	0 (0)	44643 (56.9)
UK	3749 (16.2)	10909 (34.8)	9695 (67.0)	9441 (100)	33794 (43.1)
Highest level of education attained, n (%)					
Elementary	3641 (15.7)	2558 (8.2)	871 (6.0)	663 (7.0)	7733 (9.9)
Secondary and higher	19431 (83.7)	28379 (90.6)	13255 (91.6)	8465 (89.7)	69530 (88.6)
Missing	139 (0.6)	373 (1.2)	349 (2.4)	313 (3.3)	1174 (1.5)
BMI group, n (%)					
Normal or underweight	12727 (54.8)	16296 (52.0)	6891 (47.6)	3996 (42.3)	39910 (50.9)
Overweight or obese	10241 (44.1)	14386 (45.9)	6988 (48.3)	4831 (51.2)	36446 (46.5)
Missing	243 (1.0)	628 (2.0)	596 (4.1)	614 (6.5)	2081 (2.7)
General health indicator, n (%)					
Good	20307 (87.5)	28296 (90.4)	13274 (91.7)	8734 (92.5)	70611 (90.0)
Poor	2798 (12.1)	2901 (9.3)	1175 (8.1)	707 (7.5)	7581 (9.7)
Missing	106 (0.5)	113 (0.4)	26 (0.2)	0 (0)	245 (0.3)
Sleep disturbance index, mean (SD)	27.9 (18.8)	26.2 (18.7)	25.3 (19.4)	26.1 (21.5)	26.5 (19.2)
Missing, n (%)	26 (0.1)	41 (0.1)	43 (0.3)	38 (0.4)	148 (0.2)
Painkiller use, n (%)					
No	17691 (76.2)	25918 (82.8)	12819 (88.6)	8702 (92.2)	65130 (83.0)
Yes	2832 (12.2)	3803 (12.1)	1331 (9.2)	671 (7.1)	8637 (11.0)
Missing	2688 (11.6)	1589 (5.1)	325 (2.2)	68 (0.7)	4670 (6.0)
Depression diagnosis, n (%)					
No	18044 (77.7)	25994 (83.0)	11981 (82.8)	7496 (79.4)	63515 (81.0)
Yes	2400 (10.3)	3709 (11.8)	2195 (15.2)	1881 (19.9)	10185 (13.0)
Missing	2767 (11.9)	1607 (5.1)	299 (2.1)	64 (0.7)	4737 (6.0)
High blood pressure diagnosis, n (%)					
No	15971 (68.8)	24463 (78.1)	11837 (81.8)	7969 (84.4)	60240 (76.8)
Yes	5430 (23.4)	5633 (18.0)	2368 (16.4)	1407 (14.9)	14838 (18.9)
Missing	1810 (7.8)	1214 (3.9)	270 (1.9)	65 (0.7)	3359 (4.3)
Smoking status, n (%)					
Never	11703 (50.4)	15096 (48.2)	6929 (47.9)	4618 (48.9)	38346 (48.9)
Former	9255 (39.9)	13135 (42.0)	6027 (41.6)	3729 (39.5)	32146 (41.0)
Current	2085 (9.0)	2944 (9.4)	1417 (9.8)	1002 (10.6)	7448 (9.5)
Missing	168 (0.7)	135 (0.4)	102 (0.7)	92 (1.0)	497 (0.6)
Alcohol consumption, n (%)					
Never	1393 (6.0)	1136 (3.6)	304 (2.1)	118 (1.2)	2951 (3.8)
Former	662 (2.9)	738 (2.4)	314 (2.2)	226 (2.4)	1940 (2.5)
Current	20665 (89.0)	28667 (91.6)	13169 (91.0)	8295 (87.9)	70796 (90.3)
Missing	491 (2.1)	769 (2.5)	688 (4.8)	802 (8.5)	2750 (3.5)
Weekly headache[b], n (%)					
No	20461 (88.2)	26831 (85.7)	12041 (83.2)	7525 (79.7)	66858 (85.2)
Yes	2750 (11.8)	4479 (14.3)	2434 (16.8)	1916 (20.3)	11579 (14.8)
Severe weekly headache[b], n (%)					
No	21859 (94.2)	29345 (93.7)	13552 (93.6)	8728 (92.4)	73484 (93.7)
Yes	1084 (4.7)	1743 (5.6)	866 (6.0)	705 (7.5)	4398 (5.6)
Missing	268 (1.2)	222 (0.7)	57 (0.4)	8 (0.1)	555 (0.7)
Daily headache[b], n (%)					
No	22914 (98.7)	30882 (98.6)	14238 (98.4)	9225 (97.7)	77259 (98.5)
Yes	297 (1.3)	428 (1.4)	237 (1.6)	216 (2.3)	1178 (1.5)
Migraine diagnosis[b], n (%)					
No	13611 (58.6)	21614 (69.0)	10862 (75.0)	7489 (79.3)	53576 (68.3)
Yes	2108 (9.1)	3388 (10.8)	1924 (13.3)	1513 (16.0)	8933 (11.4)
Missing	7492 (32.3)	6308 (20.1)	1689 (11.7)	439 (4.7)	15928 (20.3)

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).
[b]At baseline.

Table 2. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

		Amount of mobile phone use at baseline (call-time in categories[a])				
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.94 (0.88 – 1.01) [1432]	1 (reference) [2160]	1.08 (1.00 – 1.17) [1086]	1.10 (1.01 – 1.22) [774]	**0.002**
Weekly headache[b] (B)	66858 [5452]	0.99 (0.92 – 1.07) [1432]	1 (reference) [2160]	1.05 (0.96 – 1.13) [1086]	1.04 (0.94 – 1.15) [774]	0.292
Severe weekly headache[b] (A)	66234 [1660]	0.97 (0.86 – 1.10) [465]	1 (reference) [671]	1.08 (0.93 – 1.25) [299]	1.36 (1.13 – 1.63) [225]	**0.001**
Severe weekly headache[b] (B)	66234 [1660]	0.99 (0.87 – 1.13) [465]	1 (reference) [671]	1.05 (0.90 – 1.21) [299]	1.25 (1.04 – 1.51) [225]	**0.035**
Daily headache[b] (A)	66858 [382]	1.04 (0.79 – 1.38) [94]	1 (reference) [136]	0.98 (0.73 – 1.31) [75]	1.23 (0.90 – 1.67) [77]	0.448
Daily headache[b] (B)	66858 [382]	1.09 (0.82 – 1.46) [94]	1 (reference) [136]	0.93 (0.69 – 1.24) [75]	1.09 (0.79 – 1.50) [77]	0.900
Migraine diagnosis[c] (A)	53576 [1812]	0.93 (0.82 – 1.06) [396]	1 (reference) [725]	0.97 (0.85 – 1.11) [355]	1.19 (1.02 – 1.39) [336]	**0.013**
Migraine diagnosis[c] (B)	53576 [1812]	0.97 (0.85 – 1.11) [396]	1 (reference) [725]	0.94 (0.82 – 1.08) [355]	1.12 (0.96 – 1.30) [336]	0.247

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

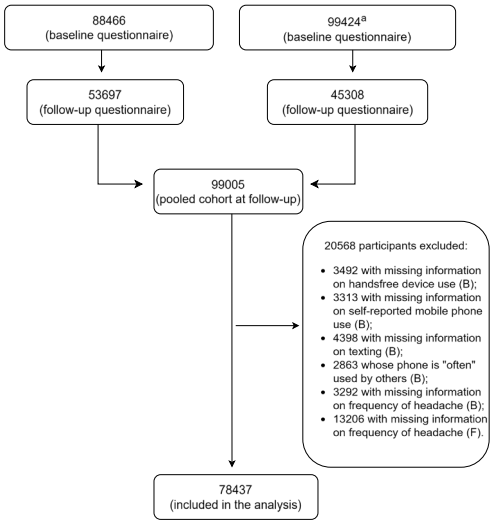
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Table 3. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.17 (1.10 – 1.26) [2012]	1.42 (1.28 – 1.58) [670]	**<0.001**
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.16 (1.08 – 1.25) [2012]	1.40 (1.25 – 1.56) [670]	**<0.001**
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.06 (0.94 – 1.20) [553]	1.63 (1.37 – 1.94) [239]	**<0.001**
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.04 (0.91 – 1.19) [553]	1.55 (1.29 – 1.87) [239]	**<0.001**
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.08 (0.84 – 1.40) [131]	1.86 (1.33 – 2.61) [70]	**<0.001**
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.12 (0.85 – 1.47) [131]	1.89 (1.33 – 2.69) [70]	**<0.001**
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.12 (1.00 – 1.26) [727]	1.51 (1.29 – 1.78) [294]	**<0.001**
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.11 (0.99 – 1.26) [727]	1.47 (1.24 – 1.75) [294]	**<0.001**

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline

Figure 1. Flowchart of the COSMOS study data.



[a]In the UK, 99424 participants provided baseline questionnaire information and 101540 consented to operator data matching out of 105028 participants recruited at baseline (14).

B=baseline questionnaire; F=follow-up questionnaire

Figure 2. Distribution of the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa) in the pooled cohort, and in the Dutch (The Netherlands (NL)) and UK sub-cohorts of COSMOS.

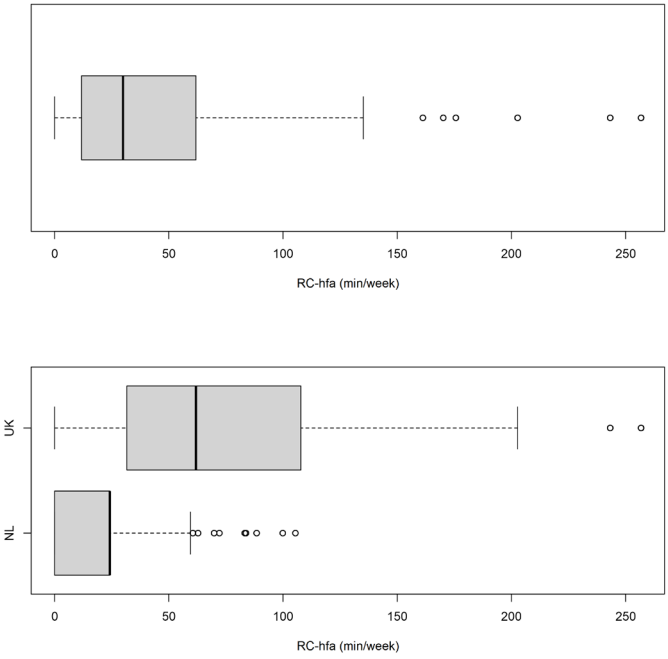
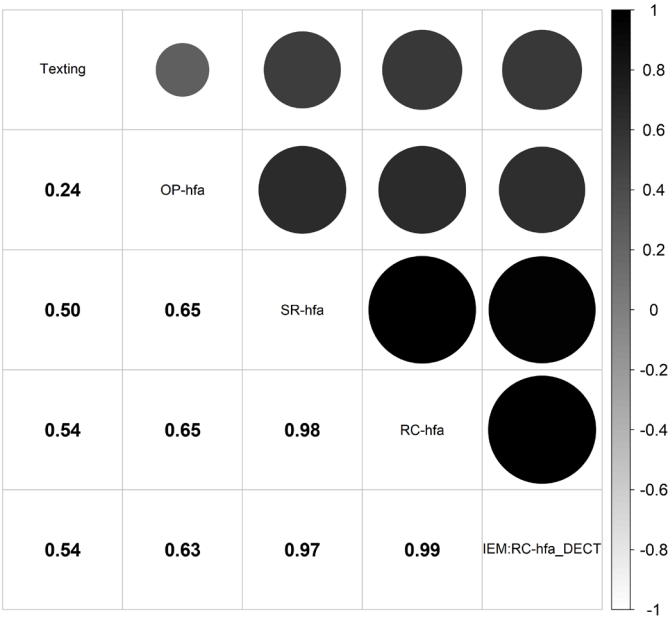


Figure 3. Spearman rank correlation coefficients and correlation plot of the exposure metrics at baseline. Darker colors and larger circles indicate higher positive correlation levels.



Texting=frequency of text messages; OP-hfa=operator-recorded call-time adjusted by the proportion of hands-free use; SR-hfa=self-reported mobile phone call-time adjusted by the proportion of hands-free use; RC-hfa= country-specific regression calibrated call-time estimates adjusted by the proportion of hands-free use; IEM:RC-hfa_DECT= RF-EMF dose (mJ/kg/week) to the brain of the participants calculated with an integrated exposure model (IEM), including country-specific regression calibrated estimates adjusted by the proportion of hands-free use (minutes/week) and cordless phone use (minutes/week).

SUPPLEMENTARY MATERIAL

Title: Headache in the international Cohort Study of Mobile Phone Use and Health (COSMOS) in the Netherlands and the United Kingdom

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Supplementary Table 29. Single-exposure (texting) and two-exposure (RC-hfa, texting) multivariable logistic regression models (complete-case analysis). Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Complete-case analysis. Number of participants with the outcome indicated in square brackets.

Exposure metrics abbreviations:

RC-hfa: country-specific regression calibrated call-time estimates adjusted by the proportion of hands-free use (minutes/week).

SR-hfa: self-reported mobile phone call-time adjusted by the proportion of hands-free use (minutes/week).

OP-hfa: operator-recorded mobile phone call-time adjusted by the proportion of hands-free use (minutes/week).

$IEM_{RC\text{-}hfa\_DECT}$: RF-EMF estimated dose (mJ/kg/week) with the integrated exposure model (IEM).

RC: country-specific regression calibrated call-time estimates (RC) (minutes/week).

Supplementary Table 1. Call-time and RF-EMF dose exposure metrics cut-offs defined on the pooled cohort at baseline (N=78437)

	Categories of exposure			
	Very low	**Low**	**Medium**	**High**
RC-hfa[a]	<19.1	19.1 – 58.5	58.6 – 107.7	107.8 – 256.8
SR-hfa[b]	<12.8	12.8 – 42.2	42.3 – 113.8	113.9 – 342.0
OP-hfa[c]	<18.5	18.5 – 73.8	73.9 – 157.7	157.8 – 1040.6
$IEM_{RC\text{-}hfa\_DECT}$[d]	<1449.0	1449.0 – 4196.0	4196.1 – 7746.1	7746.2 – 19047.05
RC[e]	<25.5	25.5 – 65.0	65.1 – 113.4	113.5 – 270.3
	Very low	**Low**	**Medium**	**High**
RC-hfa[f]	<19.1	19.1 – 58.5	58.6 – 62.7	62.8 – 256.8
RC-hfa[g]	<11.8	11.8 – 29.9	30.0 – 61.8	61.9 – 256.8

[a]Country-specific regression calibrated estimates adjusted by the proportion of hands-free use (minutes/week).
[b]Self-reported mobile phone call-time adjusted by the proportion of hands-free use (minutes/week).
[c]Operator-recorded call-time adjusted by the proportion of hands-free use (minutes/week).
[d]RF-EMF dose (mJ/kg/week) to the brain of the participants calculated with an integrated exposure model (IEM), including country-specific regression calibrated estimates adjusted by the proportion of hands-free use (minutes/week), and cordless phone call-time (minutes/week) as input data for the IEM.
[e]Country-specific regression calibrated estimates (minutes/week).
[f]Country-specific regression calibrated estimates adjusted by the proportion of hands-free use (minutes/week), with the high exposure category defined as to include both Dutch and UK participants ("high" call-time exposure category defined according to the 80th percentile).
[g]Country-specific regression calibrated estimates adjusted by the proportion of hands-free use (minutes/week), with the exposure categorised into quartiles.

Supplementary Table 2. Exposure metrics overview.

Exposure metric name (abbreviation)	Exposure metric description	Specifications
Country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)	Weekly minutes of voice calling on a mobile phone at baseline adjusted by the self-reported proportion of hands-free use, using country-specific regression calibrated estimates based on the self-report.	We replaced the ordinal indicators of self-reported voice calling in the baseline questionnaire with the average operator recorded value across all subjects at a given level of self-report. We subtracted an estimated proportion of call-time with hands-free devices from the metric based on self-report.
Self-reported mobile phone call-time adjusted by the proportion of hands-free use (SR-hfa)	Weekly minutes of voice calling on a mobile phone at baseline adjusted by the self-reported proportion of hands-free use.	Self-reported voice calling in the baseline questionnaire using midpoints of the category intervals, except the top category where *(more than) x* was set equal to *x*. We subtracted an estimated proportion of call-time with hands-free devices from the metric based on self-report.
Operator-recorded mobile phone call-time adjusted by the proportion of hands-free use (OP-hfa)	Weekly minutes of operator-recorded voice calling on a mobile phone at baseline adjusted by the self-reported proportion of hands-free use.	Providers collected information on duration of outgoing and incoming calls over a period of three months at the time the baseline questionnaire was administered. We subtracted an estimated proportion of call-time with hands-free devices from the metric based on self-report. The proportion of participants for whom complete data from network operators at baseline was available was 3% (the Netherlands) and 58% (the UK).
RF-EMF estimated dose with the integrated exposure model ($IEM_{RC\text{-}hfa\_DECT}$)	RF-EMF estimated dose (mJ/kg/week) to the brain of the participants calculated with an integrated exposure model (IEM), including country-specific regression calibrated estimates adjusted by the proportion of hands-free use (minutes/week), and cordless phone call-time (minutes/week).	In the IEM we assumed that the type of mobile phone used was 'smartphone', the proportion of time the phone was used on left/right side of the head was 50%, the proportion of time the phone was used at low (800-900 MHz) and high (1800-2100 MHz) frequencies was 0.361 (lowF), 0.639 (highF), and the proportion of time the phone was used at 2G and 3G networks was 50% (van Wel et al., 2021).
Country-specific regression calibrated estimates (RC)	Weekly minutes of voice calling on a mobile phone at baseline, using country-specific regression calibrated estimates based on self-report.	We replaced the ordinal indicators of self-reported voice calling in the baseline questionnaire with the average operator recorded value across all subjects at a given level of self-report.
Number of text messages (texting)	Self-reported number of text messages sent with a mobile phone at baseline.	-

Supplementary Table 3. Characteristics of the participants by number of text messages sent with a mobile phone at baseline.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])			
	Low (N=46190)	**Medium (N=25684)**	**High (N=6563)**	**Overall (N=78437)**
Sex, n (%)				
Men	11391 (24.7)	7629 (29.7)	2057 (31.3)	21077 (26.9)
Women	34799 (75.3)	18055 (70.3)	4506 (68.7)	57360 (73.1)
Age group (years), n (%)				
18-29	1393 (3.0)	3296 (12.8)	1924 (29.3)	6613 (8.4)
30-39	4048 (8.8)	4791 (18.7)	1346 (20.5)	10185 (13.0)
40-49	9284 (20.1)	5947 (23.2)	1505 (22.9)	16736 (21.3)
50-59	15806 (34.2)	7903 (30.8)	1343 (20.5)	25052 (31.9)
60+	15659 (33.9)	3747 (14.6)	445 (6.8)	19851 (25.3)
Country, n (%)				
The Netherlands	34036 (73.7)	9470 (36.9)	1137 (17.3)	44643 (56.9)
UK	12154 (26.3)	16214 (63.1)	5426 (82.7)	33794 (43.1)
Highest level of education attained, n (%)				
Elementary	5925 (12.8)	1347 (5.2)	461 (7.0)	7733 (9.9)
Secondary and higher	39757 (86.1)	23847 (92.8)	5926 (90.3)	69530 (88.6)
Missing	508 (1.1)	490 (1.9)	176 (2.7)	1174 (1.5)
BMI group, n (%)				
Normal or underweight	23652 (51.2)	13059 (50.8)	3199 (48.7)	39910 (50.9)
Overweight or obese	21753 (47.1)	11714 (45.6)	2979 (45.4)	36446 (46.5)
Missing	785 (1.7)	911 (3.5)	385 (5.9)	2081 (2.7)
General health indicator, n (%)				
Good	40894 (88.5)	23703 (92.3)	6014 (91.6)	70611 (90.0)
Poor	5097 (11.0)	1939 (7.5)	545 (8.3)	7581 (9.7)
Missing	199 (0.4)	42 (0.2)	4 (0.1)	245 (0.3)
Sleep disturbance index, mean (SD)	26.8 (18.7)	25.4 (19.2)	29.4 (22.3)	26.5 (19.2)
Missing, n (%)	60 (0.1)	52 (0.2)	36 (0.5)	148 (0.2)
Painkiller use, n (%)				
No	36545 (79.1)	22751 (88.6)	5834 (88.9)	65130 (83.0)
Yes	5480 (11.9)	2504 (9.7)	653 (9.9)	8637 (11.0)
Missing	4165 (9.0)	429 (1.7)	76 (1.2)	4670 (6.0)
Depression diagnosis, n (%)				
No	36905 (79.9)	21456 (83.5)	5154 (78.5)	63515 (81.0)
Yes	5034 (10.9)	3819 (14.9)	1332 (20.3)	10185 (13.0)
Missing	4251 (9.2)	409 (1.6)	77 (1.2)	4737 (6.0)
High blood pressure diagnosis, n (%)				
No	32805 (71.0)	21654 (84.3)	5781 (88.1)	60240 (76.8)
Yes	10470 (22.7)	3657 (14.2)	711 (10.8)	14838 (18.9)
Missing	2915 (6.3)	373 (1.5)	71 (1.1)	3359 (4.3)
Smoking status, n (%)				
Never	22055 (47.7)	12884 (50.2)	3407 (51.9)	38346 (48.9)
Former	19534 (42.3)	10310 (40.1)	2302 (35.1)	32146 (41.0)
Current	4316 (9.3)	2347 (9.1)	785 (12.0)	7448 (9.5)
Missing	285 (0.6)	143 (0.6)	69 (1.1)	497 (0.6)
Alcohol consumption, n (%)				
Never	2187 (4.7)	641 (2.5)	123 (1.9)	2951 (3.8)
Former	1199 (2.6)	567 (2.2)	174 (2.7)	1940 (2.5)
Current	41619 (90.1)	23402 (91.1)	5775 (88.0)	70796 (90.3)
Missing	1185 (2.6)	1074 (4.2)	491 (7.5)	2750 (3.5)
Weekly headache[b], n (%)				
No	40569 (87.8)	21347 (83.1)	4942 (75.3)	66858 (85.2)
Yes	5621 (12.2)	4337 (16.9)	1621 (24.7)	11579 (14.8)
Severe weekly headache[b], n (%)				
No	43588 (94.4)	24026 (93.5)	5870 (89.4)	73484 (93.7)
Yes	2171 (4.7)	1553 (6.0)	674 (10.3)	4398 (5.6)
Missing	431 (0.9)	105 (0.4)	19 (0.3)	555 (0.7)
Daily headache[b], n (%)				
No	45595 (98.7)	25282 (98.4)	6382 (97.2)	77259 (98.5)
Yes	595 (1.3)	402 (1.6)	181 (2.8)	1178 (1.5)
Migraine diagnosis[b], n (%)				
No	34843 (75.4)	21325 (83.0)	5256 (80.1)	61424 (78.3)
Yes	5297 (11.5)	3716 (14.5)	1198 (18.3)	10211 (13.0)
Missing	6050 (13.1)	643 (2.5)	109 (1.7)	6802 (8.7)

aLow: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
bAt baseline.

Supplementary Table 4. Characteristics of the participants in the Netherlands by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)).

	Very low (N=19462)	Low (N=20401)	Medium (N=4780)	High (N=0)	Overall (N=44643)
Sex, n (%)					
Men	1744 (9.0)	2381 (11.7)	689 (14.4)	0 (0.0)	4814 (10.8)
Wormen	17718 (91.0)	18020 (88.3)	4091 (85.6)	0 (0.0)	39829 (89.2)
Age group (years), n (%)					
18-29	309 (1.6)	1665 (8.2)	655 (13.7)	0 (0.0)	2629 (5.9)
30-39	1464 (7.5)	2623 (12.9)	790 (16.5)	0 (0.0)	4877 (10.9)
40-49	4603 (23.7)	5333 (26.1)	1244 (26.0)	0 (0.0)	11180 (25.0)
50-59	6195 (31.8)	7104 (34.8)	1656 (34.6)	0 (0.0)	14955 (33.5)
60+	6891 (35.4)	3676 (18.0)	435 (9.1)	0 (0.0)	11002 (24.6)
Highest level of education attained, n (%)					
Elementary	3354 (17.2)	1715 (8.4)	196 (4.1)	0 (0.0)	5265 (11.8)
Secondary and higher	16078 (82.6)	18649 (91.4)	4573 (95.7)	0 (0.0)	39300 (88.0)
Missing	30 (0.2)	37 (0.2)	11 (0.2)	0 (0.0)	78 (0.2)
BMI group, n (%)					
Normal or underweight	10870 (55.9)	11685 (57.3)	2873 (60.1)	0 (0.0)	25428 (57.0)
Overweight or obese	8528 (43.8)	8660 (42.4)	1897 (39.7)	0 (0.0)	19085 (42.8)
Missing	64 (0.3)	56 (0.3)	10 (0.2)	0 (0.0)	130 (0.3)
General health indicator, n (%)					
Good	16821 (86.4)	18069 (88.6)	4225 (88.4)	0 (0.0)	39115 (87.6)
Poor	2535 (13.0)	2219 (10.9)	529 (11.1)	0 (0.0)	5283 (11.8)
Missing	106 (0.5)	113 (0.6)	26 (0.5)	0 (0.0)	245 (0.5)
Sleep disturbance index, mean (SD)	28.9 (18.6)	27.7 (18.0)	27.9 (18.0)	0 (0.0)	28.2 (18.3)
Missing, n (%)	20 (0.1)	26 (0.1)	5 (0.1)	0 (0.0)	51 (0.1)
Painkiller use, n (%)					
No	14172 (72.8)	15755 (77.2)	3806 (79.6)	0 (0.0)	33733 (75.6)
Yes	2617 (13.4)	3091 (15.2)	720 (15.1)	0 (0.0)	6428 (14.4)
Missing	2673 (13.7)	1555 (7.6)	254 (5.3)	0 (0.0)	4482 (10.0)
Depression diagnosis, n (%)					
No	14925 (76.7)	17019 (83.4)	4108 (85.9)	0 (0.0)	36052 (80.8)
Yes	1782 (9.2)	1808 (8.9)	434 (9.1)	0 (0.0)	4024 (9.0)
Missing	2755 (14.2)	1574 (7.7)	238 (5.0)	0 (0.0)	4567 (10.2)
High blood pressure diagnosis, n (%)					
No	13028 (66.9)	15606 (76.5)	3865 (80.9)	0 (0.0)	32499 (72.8)
Yes	4636 (23.8)	3616 (17.7)	705 (14.7)	0 (0.0)	8957 (20.1)
Missing	1798 (9.2)	1179 (5.8)	210 (4.4)	0 (0.0)	3187 (7.1)
Smoking status, n (%)				0 (0.0)	
Never	9524 (48.9)	9513 (46.6)	2192 (45.9)	0 (0.0)	21229 (47.6)
Former	7877 (40.5)	8596 (42.1)	1915 (40.1)	0 (0.0)	18388 (41.2)
Current	1914 (9.8)	2208 (10.8)	660 (13.8)	0 (0.0)	4782 (10.7)
Missing	147 (0.8)	84 (0.4)	13 (0.3)	0 (0.0)	244 (0.5)
Alcohol consumption, n (%)					
Never	1344 (6.9)	1042 (5.1)	207 (4.3)	0 (0.0)	2593 (5.8)
Former	606 (3.1)	537 (2.6)	108 (2.3)	0 (0.0)	1251 (2.8)
Current	17323 (89.0)	18718 (91.8)	4447 (93.0)	0 (0.0)	40488 (90.7)
Missing	189 (1.0)	104 (0.5)	18 (0.4)	0 (0.0)	311 (0.7)
Weekly headache[b], n (%)					
No	17200 (88.4)	17587 (86.2)	4051 (84.7)	0 (0.0)	38838 (87.0)
Yes	2262 (11.6)	2814 (13.8)	729 (15.3)	0 (0.0)	5805 (13.0)
Severe weekly headache[b], n (%)					
No	18241 (93.7)	18922 (92.8)	4392 (91.9)	0 (0.0)	41555 (93.1)
Yes	954 (4.9)	1257 (6.2)	335 (7.0)	0 (0.0)	2546 (5.7)
Missing	267 (1.4)	222 (1.1)	53 (1.1)	0 (0.0)	542 (1.2)
Daily headache[b], n (%)					
No	19217 (98.7)	20124 (98.6)	4709 (98.5)	0 (0.0)	44050 (98.7)
Yes	245 (1.3)	277 (1.4)	71 (1.5)	0 (0.0)	593 (1.3)
Migraine diagnosis[b], n (%)					
No	10545 (54.2)	12739 (62.4)	3081 (64.5)	0 (0.0)	26365 (59.1)
Yes	1541 (7.9)	1738 (8.5)	435 (9.1)	0 (0.0)	3714 (8.3)
Missing	7376 (37.9)	5924 (29.0)	1264 (26.4)	0 (0.0)	14564 (32.6)

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).
[b]At baseline.

Supplementary Table 5. Characteristics of the participants in the UK by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)).

	Very low (N=3749)	Low (N=10909)	Medium (N=9695)	High (N=9441)	Overall (N=33794)
Sex, n (%)					
Men	1676 (44.7)	5267 (48.3)	4976 (51.3)	4344 (46.0)	16263 (48.1)
Wormen	2073 (55.3)	5642 (51.7)	4719 (48.7)	5097 (54.0)	17531 (51.9)
Age group (years), n (%)					
18-29	269 (7.2)	1085 (9.9)	1048 (10.8)	1582 (16.8)	3984 (11.8)
30-39	404 (10.8)	1682 (15.4)	1503 (15.5)	1719 (18.2)	5308 (15.7)
40-49	500 (13.3)	1649 (15.1)	1594 (16.4)	1813 (19.2)	5556 (16.4)
50-59	913 (24.4)	3218 (29.5)	3164 (32.6)	2802 (29.7)	10097 (29.9)
60+	1663 (44.4)	3275 (30.0)	2386 (24.6)	1525 (16.2)	8849 (26.2)
Highest level of education attained, n (%)					
Elementary	287 (7.7)	843 (7.7)	675 (7.0)	663 (7.0)	2468 (7.3)
Secondary and higher	3353 (89.4)	9730 (89.2)	8682 (89.6)	8465 (89.7)	30230 (89.5)
Missing	109 (2.9)	336 (3.1)	338 (3.5)	313 (3.3)	1096 (3.2)
BMI group, n (%)					
Normal or underweight	1857 (49.5)	4611 (42.3)	4018 (41.4)	3996 (42.3)	14482 (42.9)
Overweight or obese	1713 (45.7)	5726 (52.5)	5091 (52.5)	4831 (51.2)	17361 (51.4)
Missing	179 (4.8)	572 (5.2)	586 (6.0)	614 (6.5)	1951 (5.8)
General health indicator, n (%)					
Good	3486 (93.0)	10227 (93.7)	9049 (93.3)	8734 (92.5)	31496 (93.2)
Poor	263 (7.0)	682 (6.3)	646 (6.7)	707 (7.5)	2298 (6.8)
Sleep disturbance index, mean (SD)	22.7 (19.0)	23.4 (19.6)	24.0 (20.0)	26.1 (21.5)	24.3 (20.2)
Missing, n (%)	6 (0.2)	15 (0.1)	38 (0.4)	38 (0.4)	97 (0.3)
Painkiller use, n (%)					
No	3519 (93.9)	10163 (93.2)	9013 (93.0)	8702 (92.2)	31397 (92.9)
Yes	215 (5.7)	712 (6.5)	611 (6.3)	671 (7.1)	2209 (6.5)
Missing	15 (0.4)	34 (0.3)	71 (0.7)	68 (0.7)	188 (0.6)
Depression diagnosis, n (%)					
No	3119 (83.2)	8975 (82.3)	7873 (81.2)	7496 (79.4)	27463 (81.3)
Yes	618 (16.5)	1901 (17.4)	1761 (18.2)	1881 (19.9)	6161 (18.2)
Missing	12 (0.3)	33 (0.3)	61 (0.6)	64 (0.7)	170 (0.5)
High blood pressure diagnosis, n (%)					
No	2943 (78.5)	8857 (81.2)	7972 (82.2)	7969 (84.4)	27741 (82.1)
Yes	794 (21.2)	2017 (18.5)	1663 (17.2)	1407 (14.9)	5881 (17.4)
Missing	12 (0.3)	35 (0.3)	60 (0.6)	65 (0.7)	172 (0.5)
Smoking status, n (%)					
Never	2179 (58.1)	5583 (51.2)	4737 (48.9)	4618 (48.9)	17117 (50.7)
Former	1378 (36.8)	4539 (41.6)	4112 (42.4)	3729 (39.5)	13758 (40.7)
Current	171 (4.6)	736 (6.7)	757 (7.8)	1002 (10.6)	2666 (7.9)
Missing	21 (0.6)	51 (0.5)	89 (0.9)	92 (1.0)	253 (0.7)
Alcohol consumption, n (%)					
Never	49 (1.3)	94 (0.9)	97 (1.0)	118 (1.2)	358 (1.1)
Former	56 (1.5)	201 (1.8)	206 (2.1)	226 (2.4)	689 (2.0)
Current	3342 (89.1)	9949 (91.2)	8722 (90.0)	8295 (87.9)	30308 (89.7)
Missing	302 (8.1)	665 (6.1)	670 (6.9)	802 (8.5)	2439 (7.2)
Weekly headache[b], n (%)					
No	3261 (87.0)	9244 (84.7)	7990 (82.4)	7525 (79.7)	28020 (82.9)
Yes	488 (13.0)	1665 (15.3)	1705 (17.6)	1916 (20.3)	5774 (17.1)
Severe weekly headache[b], n (%)					
No	3618 (96.5)	10423 (95.5)	9160 (94.5)	8728 (92.4)	31929 (94.5)
Yes	130 (3.5)	486 (4.5)	531 (5.5)	705 (7.5)	1852 (5.5)
Missing	1 (0.0)	0 (0)	4 (0.0)	8 (0.1)	13 (0.0)
Daily headache[b], n (%)					
No	3697 (98.6)	10758 (98.6)	9529 (98.3)	9225 (97.7)	33209 (98.3)
Yes	52 (1.4)	151 (1.4)	166 (1.7)	216 (2.3)	585 (1.7)
Migraine diagnosis[b], n (%)					
No	3066 (81.8)	8875 (81.4)	7781 (80.3)	7489 (79.3)	27211 (80.5)
Yes	567 (15.1)	1650 (15.1)	1489 (15.4)	1513 (16.0)	5219 (15.4)
Missing	116 (3.1)	384 (3.5)	425 (4.4)	439 (4.6)	1364 (4.0)

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).
[b]At baseline.

Supplementary Table 6. Characteristics of the participants in the Netherlands by number of text messages sent with a mobile phone at baseline.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])			
	Low (N=34036)	**Medium (N=9470)**	**High (N=1137)**	**Overall (N=44643)**
Sex, n (%)				
Men	4093 (12.0)	643 (6.8)	78 (6.9)	4814 (10.8)
Women	29943 (88.0)	8827 (93.2)	1059 (93.1)	39829 (89.2)
Age group (years), n (%)				
18-29	933 (2.7)	1388 (14.7)	308 (27.1)	2629 (5.9)
30-39	2917 (8.6)	1724 (18.2)	236 (20.8)	4877 (10.9)
40-49	7860 (23.1)	2997 (31.6)	323 (28.4)	11180 (25.0)
50-59	11945 (35.1)	2787 (29.4)	223 (19.6)	14955 (33.5)
60+	10381 (30.5)	574 (6.1)	47 (4.1)	11002 (24.6)
Highest level of education attained, n (%)				
Elementary	4898 (14.4)	326 (3.4)	41 (3.6)	5265 (11.8)
Secondary and higher	29082 (85.4)	9124 (96.3)	1094 (96.2)	39300 (88.0)
Missing	56 (0.2)	20 (0.2)	2 (0.2)	78 (0.2)
BMI group, n (%)				
Normal or under-weight	18929 (55.6)	5802 (61.3)	697 (61.3)	25428 (57.0)
Overweight or obese	15004 (44.1)	3643 (38.5)	438 (38.5)	19085 (42.8)
Missing	103 (0.3)	25 (0.3)	2 (0.2)	130 (0.3)
General health indicator, n (%)				
Good	29626 (87.0)	8501 (89.8)	988 (86.9)	39115 (87.6)
Poor	4211 (12.4)	927 (9.8)	145 (12.8)	5283 (11.8)
Missing	199 (0.6)	42 (0.4)	4 (0.4)	245 (0.5)
Sleep disturbance index, mean (SD)	28.4 (18.4)	27.5 (17.8)	29.1 (19.2)	28.2 (18.3)
Missing, n (%)	34 (0.1)	12 (0.1)	5 (0.4)	51 (0.1)
Painkiller use, n (%)				
No	25230 (74.1)	7641 (80.7)	862 (75.8)	33733 (75.6)
Yes	4702 (13.8)	1483 (15.7)	243 (21.4)	6428 (14.4)
Missing	4104 (12.1)	346 (3.7)	32 (2.8)	4482 (10.0)
Depression diagnosis, n (%)				
No	26697 (78.4)	8350 (88.2)	1005 (88.4)	36052 (80.8)
Yes	3141 (9.2)	785 (8.3)	98 (8.6)	4024 (9.0)
Missing	4198 (12.3)	335 (3.5)	34 (3.0)	4567 (10.2)
High blood pressure diagnosis, n (%)				
No	23599 (69.3)	7923 (83.7)	977 (85.9)	32499 (72.8)
Yes	7578 (22.3)	1248 (13.2)	131 (11.5)	8957 (20.1)
Missing	2859 (8.4)	299 (3.2)	29 (2.6)	3187 (7.1)
Smoking status, n (%)				
Never	15953 (46.9)	4675 (49.4)	601 (52.9)	21229 (47.6)
Former	14342 (42.1)	3679 (38.8)	367 (32.3)	18388 (41.2)
Current	3533 (10.4)	1087 (11.5)	162 (14.2)	4782 (10.7)
Missing	208 (0.6)	29 (0.3)	7 (0.6)	244 (0.5)
Alcohol consumption, n (%)				
Never	2057 (6.0)	477 (5.0)	59 (5.2)	2593 (5.8)
Former	992 (2.9)	231 (2.4)	28 (2.5)	1251 (2.8)
Current	30703 (90.2)	8737 (92.3)	1048 (92.2)	40488 (90.7)
Missing	284 (0.8)	25 (0.3)	2 (0.2)	311 (0.7)
Weekly headache[b], n (%)				
No	29974 (88.1)	7960 (84.1)	904 (79.5)	38838 (87.0)
Yes	4062 (11.9)	1510 (15.9)	233 (20.5)	5805 (13.0)
Severe weekly headache[b], n (%)				
No	31856 (93.6)	8694 (91.8)	1005 (88.4)	41555 (93.1)
Yes	1752 (5.1)	675 (7.1)	119 (10.5)	2546 (5.7)
Missing	428 (1.3)	101 (1.1)	13 (1.1)	542 (1.2)
Daily headache[b], n (%)				
No	33609 (98.7)	9328 (98.5)	1113 (97.9)	44050 (98.7)
Yes	427 (1.3)	142 (1.5)	24 (2.1)	593 (1.3)
Migraine diagnosis[b], n (%)				
No	18869 (55.4)	6714 (70.9)	782 (68.8)	26365 (59.1)
Yes	2682 (7.9)	886 (9.4)	146 (12.8)	3714 (8.3)
Missing	12485 (36.7)	1870 (19.7)	209 (18.4)	14564 (32.6)

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]At baseline.

Supplementary Table 7. Characteristics of the participants in the UK by number of text messages sent with a mobile phone at baseline.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])			
	Low (N=12154)	**Medium (N=16214)**	**High (N=5426)**	**Overall (N=33794)**
Sex, n (%)				
Men	7298 (60.0)	6986 (43.1)	1979 (36.5)	16263 (48.1)
Women	4856 (40.0)	9228 (56.9)	3447 (63.5)	17531 (51.9)
Age group (years), n (%)				
18-29	460 (3.8)	1908 (11.8)	1616 (29.8)	3984 (11.8)
30-39	1131 (9.3)	3067 (18.9)	1110 (20.5)	5308 (15.7)
40-49	1424 (11.7)	2950 (18.2)	1182 (21.8)	5556 (16.4)
50-59	3861 (31.8)	5116 (31.6)	1120 (20.6)	10097 (29.9)
60+	5278 (43.4)	3173 (19.6)	398 (7.3)	8849 (26.2)
Highest level of education attained, n (%)				
Elementary	1027 (8.4)	1021 (6.3)	420 (7.7)	2468 (7.3)
Secondary and higher	10675 (87.8)	14723 (90.8)	4832 (89.1)	30230 (89.5)
Missing	452 (3.7)	470 (2.9)	174 (3.2)	1096 (3.2)
BMI group, n (%)				
Normal or underweight	4723 (38.9)	7257 (44.8)	2502 (46.1)	14482 (42.9)
Overweight or obese	6749 (55.5)	8071 (49.8)	2541 (46.8)	17361 (51.4)
Missing	682 (5.6)	886 (5.5)	383 (7.1)	1951 (5.8)
General health indicator, n (%)				
Good	11268 (92.7)	15202 (93.8)	5026 (92.6)	31496 (93.2)
Poor	886 (7.3)	1012 (6.2)	400 (7.4)	2298 (6.8)
Sleep disturbance index, mean (SD)	22.2 (19.0)	24.1 (19.9)	29.5 (22.9)	24.3 (20.2)
Missing, n (%)	26 (0.2)	40 (0.2)	31 (0.6)	97 (0.3)
Painkiller use, n (%)				
No	11315 (93.1)	15110 (93.2)	4972 (91.6)	31397 (92.9)
Yes	778 (6.4)	1021 (6.3)	410 (7.6)	2209 (6.5)
Missing	61 (0.5)	83 (0.5)	44 (0.8)	188 (0.6)
Depression diagnosis, n (%)				
No	10208 (84.0)	13106 (80.8)	4149 (76.5)	27463 (81.3)
Yes	1893 (15.6)	3034 (18.7)	1234 (22.7)	6161 (18.2)
Missing	53 (0.4)	74 (0.5)	43 (0.8)	170 (0.5)
High blood pressure diagnosis, n (%)				
No	9206 (75.7)	13731 (84.7)	4804 (88.5)	27741 (82.1)
Yes	2892 (23.8)	2409 (14.9)	580 (10.7)	5881 (17.4)
Missing	56 (0.5)	74 (0.5)	42 (0.8)	172 (0.5)
Smoking status, n (%)				
Never	6102 (50.2)	8209 (50.6)	2806 (51.7)	17117 (50.7)
Former	5192 (42.7)	6631 (40.9)	1935 (35.7)	13758 (40.7)
Current	783 (6.4)	1260 (7.8)	623 (11.5)	2666 (7.9)
Missing	77 (0.6)	114 (0.7)	62 (1.1)	253 (0.7)
Alcohol consumption, n (%)				
Never	130 (1.1)	164 (1.0)	64 (1.2)	358 (1.1)
Former	207 (1.7)	336 (2.1)	146 (2.7)	689 (2.0)
Current	10916 (89.8)	14665 (90.4)	4727 (87.1)	30308 (89.7)
Missing	901 (7.4)	1049 (6.5)	489 (9.0)	2439 (7.2)
Weekly headache[b], n (%)				
No	10595 (87.2)	13387 (82.6)	4038 (74.4)	28020 (82.9)
Yes	1559 (12.8)	2827 (17.4)	1388 (25.6)	5774 (17.1)
Severe weekly headache[b], n (%)				
No	11732 (96.5)	15332 (94.6)	4865 (89.7)	31929 (94.5)
Yes	419 (3.4)	878 (5.4)	555 (10.2)	1852 (5.5)
Missing	3 (0.0)	4 (0.0)	6 (0.1)	13 (0.0)
Daily headache[b], n (%)				
No	11986 (98.6)	15954 (98.4)	5269 (97.1)	33209 (98.3)
Yes	168 (1.4)	260 (1.6)	157 (2.9)	585 (1.7)
Migraine diagnosis[b], n (%)				
No	10046 (82.7)	13025 (80.3)	4140 (76.3)	27211 (80.5)
Yes	1698 (14.0)	2538 (15.7)	983 (18.1)	5219 (15.4)
Missing	410 (3.4)	651 (4.0)	303 (5.6)	1364 (4.0)

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]At baseline.

Supplementary Table 8. Characteristics of the participants who completed the baseline questionnaire (irrespective of their subsequent completion of the follow-up questionnaire) by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)).

	Amount of mobile phone use at baseline (call-time in categories[a])				
	Very low (N=42322)	**Low (N=61078)**	**Medium (N=34134)**	**High (N=28136)**	**Overall[b] (N=165670)**
Sex, n (%)					
Men	6849 (16.2)	16534 (27.1)	13826 (40.5)	12744 (45.3)	49953 (30.2)
Women	35472 (83.8)	44537 (72.9)	20306 (59.5)	15389 (54.7)	115704 (69.8)
Missing	1 (0.0)	7 (0.0)	2 (0.0)	3 (0.0)	13 (0.0)
Age group (years), n (%)					
18-29	1674 (4.0)	7744 (12.7)	6176 (18.1)	7434 (26.4)	23028 (13.9)
30-39	4097 (9.7)	9783 (16.0)	6410 (18.8)	5921 (21.0)	26211 (15.8)
40-49	9607 (22.7)	13763 (22.5)	6604 (19.3)	5185 (18.4)	35159 (21.2)
50-59	12255 (29.0)	17701 (29.0)	9369 (27.4)	6246 (22.2)	45571 (27.5)
60+	14686 (34.7)	12076 (19.8)	5565 (16.3)	3328 (11.8)	35655 (21.5)
Missing	3 (0.0)	11 (0.0)	10 (0.0)	22 (0.1)	46 (0.0)
Country, n (%)					
The Netherlands	34014 (80.4)	34899 (57.1)	9136 (26.8)	0 (0)	78049 (47.1)
UK	8308 (19.6)	26179 (42.9)	24998 (73.2)	28136 (100)	87621 (52.9)
Highest level of education attained, n (%)					
Elementary	7569 (17.9)	5910 (9.7)	2867 (8.4)	2870 (10.2)	19216 (11.6)
Secondary and higher	34237 (80.9)	53640 (87.8)	29799 (87.3)	23425 (83.3)	141101 (85.2)
Missing	516 (1.2)	1528 (2.5)	1468 (4.3)	1841 (6.5)	5353 (3.2)
BMI group, n (%)					
Normal or underweight	21607 (51.1)	28733 (47.0)	13720 (40.2)	9556 (34.0)	73616 (44.4)
Overweight or obese	18739 (44.3)	26104 (42.7)	14091 (41.3)	10982 (39.0)	69916 (42.2)
Missing	1976 (4.7)	6241 (10.2)	6323 (18.5)	7598 (27.0)	22138 (13.4)
General health indicator, n (%)					
Good	36236 (85.6)	54697 (89.6)	31094 (91.1)	25644 (91.1)	147671 (89.1)
Poor	5855 (13.8)	6176 (10.1)	2996 (8.8)	2492 (8.9)	17519 (10.6)
Missing	231 (0.5)	205 (0.3)	44 (0.1)	0 (0)	480 (0.3)
Sleep disturbance index, mean (SD)	28.1 (19.4)	26.7 (19.4)	26.6 (20.6)	28.8 (23.1)	27.4 (20.3)
Missing, n (%)	109 (0.3)	228 (0.4)	217 (0.6)	264 (0.9)	818 (0.5)
Painkiller use, n (%)					
No	32335 (76.4)	50807 (83.2)	29994 (87.9)	25378 (90.2)	138514 (83.6)
Yes	5444 (12.9)	7537 (12.3)	3306 (9.7)	2241 (8.0)	18528 (11.2)
Missing	4543 (10.7)	2734 (4.5)	834 (2.4)	517 (1.8)	8628 (5.2)
Depression diagnosis, n (%)					
No	33062 (78.1)	50505 (82.7)	27830 (81.5)	21931 (77.9)	133328 (80.5)
Yes	4592 (10.9)	7853 (12.9)	5522 (16.2)	5746 (20.4)	23713 (14.3)
Missing	4668 (11.0)	2720 (4.5)	782 (2.3)	459 (1.6)	8629 (5.2)
High blood pressure diagnosis, n (%)					
No	29547 (69.8)	48430 (79.3)	28242 (82.7)	24034 (85.4)	130253 (78.6)
Yes	9760 (23.1)	10496 (17.2)	5165 (15.1)	3643 (12.9)	29064 (17.5)
Missing	3015 (7.1)	2152 (3.5)	727 (2.1)	459 (1.6)	6353 (3.8)
Smoking status, n (%)					
Never	20822 (49.2)	29152 (47.7)	15962 (46.8)	13141 (46.7)	79077 (47.7)
Former	16647 (39.3)	24456 (40.0)	13393 (39.2)	10106 (35.9)	64602 (39.0)
Current	4447 (10.5)	6895 (11.3)	4262 (12.5)	4192 (14.9)	19796 (11.9)
Missing	406 (1.0)	575 (0.9)	517 (1.5)	697 (2.5)	2195 (1.3)
Alcohol consumption, n (%)					
Never	2702 (6.4)	2183 (3.6)	715 (2.1)	362 (1.3)	5962 (3.6)
Former	1336 (3.2)	1648 (2.7)	876 (2.6)	832 (3.0)	4692 (2.8)
Current	36996 (87.4)	54852 (89.8)	30139 (88.3)	23639 (84.0)	145626 (87.9)
Missing	1288 (3.0)	2395 (3.9)	2404 (7.0)	3303 (11.7)	9390 (5.7)
Weekly headache[c], n (%)					
No	36630 (86.6)	51102 (83.7)	27592 (80.8)	21311 (75.7)	136635 (82.5)
Yes	5692 (13.4)	9976 (16.3)	6542 (19.2)	6825 (24.3)	29035 (17.5)
Severe weekly headache[c], n (%)					
No	39387 (93.1)	56673 (92.8)	31601 (92.6)	25389 (90.2)	153050 (92.4)
Yes	2383 (5.6)	3941 (6.5)	2399 (7.0)	2691 (9.6)	11414 (6.9)
Missing	552 (1.3)	464 (0.8)	134 (0.4)	56 (0.2)	1206 (0.7)
Daily headache[c], n (%)					
No	41610 (98.3)	60068 (98.3)	33457 (98.0)	27307 (97.1)	162442 (98.1)
Yes	712 (1.7)	1010 (1.7)	677 (2.0)	829 (2.9)	3228 (1.9)
Migraine diagnosis[c], n (%)					
No	31028 (73.3)	49522 (81.1)	28201 (82.6)	23130 (82.2)	131881 (79.6)
Yes	4776 (11.3)	7703 (12.6)	4863 (14.2)	4545 (16.2)	21887 (13.2)
Missing	6519 (15.4)	3852 (6.3)	1070 (3.1)	461 (1.6)	11902 (7.2)

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).
[b]After exclusion of participants with missing information on handsfree device use (N=8568), self-reported mobile phone use (N=8098), texting (N=10734), frequency of headache at baseline (N=10508), and finally participants whose phone was "often" used by others (N=5681).
[c]At baseline.

Supplementary Table 9. Characteristics of the participants who completed the baseline questionnaire (irrespective of their subsequent completion of the follow-up questionnaire) by number of text messages sent with a mobile phone at baseline.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])			
	Low (N=85534)	**Medium (N=57580)**	**High (N=22556)**	**Overall[b] (N=165670)**
Sex, n (%)				
Men	23324 (27.3)	18595 (32.3)	8034 (35.6)	49953 (30.2)
Women	62203 (72.7)	38980 (67.7)	14521 (64.4)	115704 (69.8)
Missing	7 (0.0)	5 (0.0)	1 (0.0)	13 (0.0)
Age group (years), n (%)				
18-29	3941 (4.6)	9926 (17.2)	9161 (40.6)	23028 (13.9)
30-39	9210 (10.8)	12331 (21.4)	4670 (20.7)	26211 (15.8)
40-49	17671 (20.7)	13086 (22.7)	4402 (19.5)	35159 (21.2)
50-59	27362 (32.0)	14951 (26.0)	3258 (14.4)	45571 (27.5)
60+	27337 (32.0)	7269 (12.6)	1049 (4.7)	35655 (21.5)
Missing	13 (0.0)	17 (0.0)	16 (0.1)	46 (0.0)
Country, n (%)				
The Netherlands	57967 (67.8)	17605 (30.6)	2477 (11.0)	78049 (47.1)
UK	27567 (32.2)	39975 (69.4)	20079 (89.0)	87621 (52.9)
Highest level of education attained, n (%)				
Elementary	12676 (14.8)	4266 (7.4)	2274 (10.1)	19216 (11.6)
Secondary and higher	70886 (82.9)	51160 (88.9)	19055 (84.5)	141101 (85.2)
Missing	1972 (2.3)	2154 (3.7)	1227 (5.4)	5353 (3.2)
BMI group, n (%)				
Normal or under-weight	39632 (46.3)	24888 (43.2)	9096 (40.3)	73616 (44.4)
Overweight or obese	38843 (45.4)	22824 (39.6)	8249 (36.6)	69916 (42.2)
Missing	7059 (8.3)	9868 (17.1)	5211 (23.1)	22138 (13.4)
General health indicator, n (%)				
Good	74378 (87.0)	52705 (91.5)	20588 (91.3)	147671 (89.1)
Poor	10765 (12.6)	4796 (8.3)	1958 (8.7)	17519 (10.6)
Missing	391 (0.5)	79 (0.1)	10 (0.0)	480 (0.3)
Sleep disturbance index, mean (SD)	27.0 (19.4)	26.4 (20.1)	31.2 (23.6)	27.4 (20.3)
Missing, n (%)	285 (0.3)	295 (0.5)	238 (1.1)	818 (0.5)
Painkiller use, n (%)				
No	67940 (79.4)	50716 (88.1)	19858 (88.0)	138514 (83.6)
Yes	10591 (12.4)	5711 (9.9)	2226 (9.9)	18528 (11.2)
Missing	7003 (8.2)	1153 (2.0)	472 (2.1)	8628 (5.2)
Depression diagnosis, n (%)				
No	68444 (80.0)	47323 (82.2)	17561 (77.9)	133328 (80.5)
Yes	9975 (11.7)	9178 (15.9)	4560 (20.2)	23713 (14.3)
Missing	7115 (8.3)	1079 (1.9)	435 (1.9)	8629 (5.2)
High blood pressure diagnosis, n (%)				
No	61370 (71.7)	48858 (84.9)	20025 (88.8)	130253 (78.6)
Yes	19258 (22.5)	7703 (13.4)	2103 (9.3)	29064 (17.5)
Missing	4906 (5.7)	1019 (1.8)	428 (1.9)	6353 (3.8)
Smoking status, n (%)				
Never	39828 (46.6)	27954 (48.5)	11295 (50.1)	79077 (47.7)
Former	35190 (41.1)	22238 (38.6)	7174 (31.8)	64602 (39.0)
Current	9632 (11.3)	6631 (11.5)	3533 (15.7)	19796 (11.9)
Missing	884 (1.0)	757 (1.3)	554 (2.5)	2195 (1.3)
Alcohol consumption, n (%)				
Never	4182 (4.9)	1400 (2.4)	380 (1.7)	5962 (3.6)
Former	2488 (2.9)	1470 (2.6)	734 (3.3)	4692 (2.8)
Current	75178 (87.9)	51232 (89.0)	19216 (85.2)	145626 (87.9)
Missing	3686 (4.3)	3478 (6.0)	2226 (9.9)	9390 (5.7)
Weekly headache[c], n (%)				
No	73667 (86.1)	46745 (81.2)	16223 (71.9)	136635 (82.5)
Yes	11867 (13.9)	10835 (18.8)	6333 (28.1)	29035 (17.5)
Severe weekly headache[c], n (%)				
No	79907 (93.4)	53322 (92.6)	19821 (87.9)	153050 (92.4)
Yes	4745 (5.5)	4013 (7.0)	2656 (11.8)	11414 (6.9)
Missing	882 (1.0)	245 (0.4)	79 (0.4)	1206 (0.7)
Daily headache[c], n (%)				
No	84176 (98.4)	56513 (98.1)	21753 (96.4)	162442 (98.1)
Yes	1358 (1.6)	1067 (1.9)	803 (3.6)	3228 (1.9)
Migraine diagnosis[c], n (%)				
No	65738 (76.9)	47863 (83.1)	18280 (81.0)	131881 (79.6)
Yes	9797 (11.5)	8294 (14.4)	3796 (16.8)	21887 (13.2)
Missing	10000 (11.7)	1422 (2.5)	480 (2.1)	11902 (7.2)

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]After exclusion of participants with missing information on handsfree device use (N=8568), self-reported mobile phone use (N=8098), texting (N=10734), frequency of headache at baseline (N=10508), and finally participants whose phone was "often" used by others (N=5681).
[c]At baseline.

Supplementary Table 10. Single-exposure (RC-hfa) multivariable logistic regression models stratified by sex, age group, country.
Odds ratio (OR) with 95% CI for weekly headache at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)), stratified by sex, age group, country. Excluding participants with weekly headache at baseline. Number of participants with the outcome indicated in square brackets.

	Amount of mobile phone use at baseline (call-time in categories[a])				
	Very low	**Low**	**Medium**	**High**	**P interaction**
Sex[b]					Sex:RC-hfa
Men	1.00 (0.82 – 1.22) [155]	1 (reference) [398]	1.02 (0.88 – 1.20) [323]	1.15 (0.98 – 1.36) [302]	0.480
Women	0.94 (0.87 – 1.01) [1277]	1 (reference) [1762]	1.10 (1.00 – 1.21) [763]	1.07 (0.94 – 1.21) [472]	
Age group[b]					Age group:RC-hfa
18-29	1.03 (0.76 – 1.39) [63]	1 (reference) [286]	0.91 (0.73 – 1.12) [172]	0.83 (0.65 – 1.05) [153]	0.103
30-39	0.96 (0.79 – 1.17) [168]	1 (reference) [385]	1.03 (0.86 – 1.24) [211]	1.14 (0.92 – 1.42) [167]	
40-49	1.09 (0.95 – 1.25) [405]	1 (reference) [512]	1.20 (1.02 – 1.43) [251]	1.25 (1.01 – 1.54) [177]	
50-59	0.88 (0.77 – 1.01) [406]	1 (reference) [633]	1.15 (0.99 – 1.34) [313]	1.23 (1.02 – 1.49) [194]	
60+	0.88 (0.75 – 1.03) [390]	1 (reference) [344]	1.01 (0.82 – 1.26) [139]	1.09 (0.84 – 1.42) [83]	
Country[b]					Country:RC-hfa
The Netherlands	0.93 (0.86 – 1.02) [1190]	1 (reference) [1403]	1.09 (0.97 – 1.23) [374]	NA [0]	0.611
The United Kingdom	0.99 (0.85 – 1.15) [242]	1 (reference) [757]	1.07 (0.96 – 1.19) [712]	1.11 (1.00 – 1.24) [774]	

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).
[b]Models adjusted for highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, alcohol consumption, and mutually adjusted for sex, age group, country at baseline.

Supplementary Table 11. Single-exposure (texting) multivariable logistic regression models stratified by sex, age group, country.
Odds ratio (OR) with 95% CI for weekly headache at follow-up by number of text messages sent with a mobile phone at baseline, stratified by sex, age group, country. Excluding participants with weekly headache at baseline. Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])			
	Low	**Medium**	**High**	**P interaction**
Sex[b]				Sex:Text messages
Men	1 (reference) [522]	1.09 (0.93 – 1.28) [461]	1.58 (1.23 – 2.04) [195]	0.461
Women	1 (reference) [2248]	1.19 (1.09 – 1.29) [1551]	1.52 (1.32 – 1.76) [475]	
Age group[b]				Age group:Text messages
18-29	1 (reference) [130]	0.94 (0.75 – 1.19) [245]	1.40 (1.06 – 1.84) [146]	0.448
30-39	1 (reference) [311]	1.18 (0.99 – 1.40) [356]	1.69 (1.30 – 2.21) [97]	
40-49	1 (reference) [660]	1.10 (0.96 – 1.26) [411]	1.34 (1.05 – 1.71) [97]	
50-59	1 (reference) [845]	1.37 (1.20 – 1.55) [441]	1.59 (1.21 – 2.10) [66]	
60+	1 (reference) [702]	1.07 (0.88 – 1.31) [151]	1.48 (0.91 – 2.40) [20]	
Country[b]				Country:Text messages
The Netherlands	1 (reference) [2082]	1.19 (1.09 – 1.31) [772]	1.39 (1.12 – 1.71) [113]	0.295
The United Kingdom	1 (reference) [688]	1.15 (1.02 – 1.29) [1240]	1.62 (1.37 – 1.90) [557]	

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]Models adjusted for highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, alcohol consumption, and mutually adjusted for sex, age group, country at baseline.

Supplementary Table 12. Single-exposure (SR-hfa) and two-exposure (SR-hfa, texting) multivariable logistic regression models.
Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, self-reported mobile phone use adjusted by the proportion of hands-free use (SR-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

	Amount of mobile phone use at baseline (call-time in categories[a])					
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.97 (0.90 – 1.04) [1457]	1 (reference) [1849]	1.07 (0.98 – 1.16) [1017]	1.13 (1.04 – 1.22) [1129]	<0.001
Weekly headache[b] (B)	66858 [5452]	1.01 (0.93 – 1.09) [1457]	1 (reference) [1849]	1.04 (0.96 – 1.13) [1017]	1.07 (0.99 – 1.17) [1129]	0.167
Severe weekly headache[b] (A)	66234 [1660]	1.04 (0.91 – 1.19) [474]	1 (reference) [530]	1.10 (0.95 – 1.28) [288]	1.35 (1.18 – 1.56) [368]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1.06 (0.92 – 1.21) [474]	1 (reference) [530]	1.08 (0.93 – 1.26) [288]	1.28 (1.11 – 1.48) [368]	0.016
Daily headache[b] (A)	66858 [382]	1.14 (0.86 – 1.51) [98]	1 (reference) [119]	1.04 (0.77 – 1.40) [71]	1.25 (0.95 – 1.66) [94]	0.532
Daily headache[b] (B)	66858 [382]	1.18 (0.88 – 1.58) [98]	1 (reference) [119]	0.99 (0.73 – 1.34) [71]	1.14 (0.85 – 1.52) [94]	0.838
Migraine diagnosis[c] (A)	53576 [1812]	0.92 (0.81 – 1.05) [402]	1 (reference) [651]	0.94 (0.82 – 1.08) [335]	1.06 (0.93 – 1.21) [424]	0.146
Migraine diagnosis[c] (B)	53576 [1812]	0.96 (0.84 – 1.10) [402]	1 (reference) [651]	0.92 (0.80 – 1.05) [335]	1.00 (0.88 – 1.15) [424]	0.860

[a]Very low: SR-hfa < 12.8 (min/week); Low: SR-hfa ≥ 12.8 & SR-hfa < 42.3 (min/week); Medium: SR-hfa ≥ 42.3 & SR-hfa < 113.9 (min/week); High: SR-hfa ≥ 113.9 (min/week), (max=342.0 min/week).
[b]Models adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Models adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 13. Single-exposure (texting) and two-exposure (SR-hfa, texting) multivariable logistic regression models.
Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, self-reported mobile phone use adjusted by the proportion of hands-free use (SR-hfa)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.17 (1.10 – 1.26) [2012]	1.42 (1.28 – 1.58) [670]	<0.001
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.16 (1.08 – 1.25) [2012]	1.39 (1.25 – 1.55) [670]	<0.001
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.06 (0.94 – 1.20) [553]	1.63 (1.37 – 1.94) [239]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.03 (0.91 – 1.18) [553]	1.54 (1.28 – 1.84) [239]	<0.001
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.08 (0.84 – 1.40) [131]	1.86 (1.33 – 2.61) [70]	<0.001
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.12 (0.85 – 1.47) [131]	1.88 (1.32 – 2.68) [70]	<0.001
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.12 (1.00 – 1.26) [727]	1.51 (1.29 – 1.78) [294]	<0.001
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.12 (0.99 – 1.26) [727]	1.50 (1.27 – 1.78) [294]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 14. Single-exposure (OP-hfa) and two-exposure (OP-hfa, texting) multivariable logistic regression models.
Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, operator-recorded data adjusted by the proportion of hands-free use (OP-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

	Amount of mobile phone use at baseline (call-time in categories[a])					
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	16213 [1429]	0.96 (0.84 – 1.10) [405]	1 (reference) [569]	1.05 (0.91 – 1.23) [290]	1.12 (0.93 – 1.35) [165]	0.107
Weekly headache[b] (B)	16213 [1429]	1.01 (0.88 – 1.16) [405]	1 (reference) [569]	1.03 (0.88 – 1.19) [290]	1.07 (0.89 – 1.29) [165]	0.519
Severe weekly headache[b] (A)	16170 [352]	0.87 (0.67 – 1.13) [95]	1 (reference) [147]	0.92 (0.68 – 1.25) [62]	1.30 (0.92 – 1.83) [48]	0.056
Severe weekly headache[b] (B)	16170 [352]	0.93 (0.71 – 1.21) [95]	1 (reference) [147]	0.87 (0.64 – 1.19) [62]	1.20 (0.85 – 1.70) [48]	0.289
Daily headache[b] (A)	16213 [124]	1.08 (0.70 – 1.66) [37]	1 (reference) [48]	0.91 (0.55 – 1.51) [23]	1.16 (0.65 – 2.06) [16]	0.893
Daily headache[b] (B)	16213 [124]	1.14 (0.73 – 1.76) [37]	1 (reference) [48]	0.87 (0.52 – 1.44) [23]	1.05 (0.58 – 1.87) [16]	0.690
Migraine diagnosis[c] (A)	15421 [563]	0.99 (0.80 – 1.23) [158]	1 (reference) [214]	1.21 (0.96 – 1.52) [130]	1.03 (0.77 – 1.39) [61]	0.534
Migraine diagnosis[c] (B)	15421 [563]	1.01 (0.82 – 1.26) [158]	1 (reference) [214]	1.19 (0.95 – 1.50) [130]	1.01 (0.75 – 1.36) [61]	0.759

[a]Very low: OP-hfa < 18.5 (min/week); Low: OP-hfa ≥ 18.5 & OP-hfa < 73.9 (min/week); Medium: OP-hfa ≥ 73.9 & OP-hfa < 157.8 (min/week); High: OP-hfa ≥ 157.8 (min/week), (max=1040.6 min/week).
[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 15. Single-exposure (texting) and two-exposure (OP-hfa, texting) multivariable logistic regression models.
Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, operator-recorded data adjusted by the proportion of hands-free use (OP-hfa)). Number of participants with the outcome indicated in square brackets

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	16213 [1429]	1 (reference) [358]	1.23 (1.07 – 1.42) [751]	1.59 (1.33 – 1.89) [320]	<0.001
Weekly headache[b] (B)	16213 [1429]	1 (reference) [358]	1.23 (1.07 – 1.42) [751]	1.57 (1.31 – 1.89) [320]	<0.001
Severe weekly headache[b] (A)	16170 [352]	1 (reference) [69]	1.40 (1.04 – 1.89) [182]	2.11 (1.49 – 2.99) [101]	<0.001
Severe weekly headache[b] (B)	16170 [352]	1 (reference) [69]	1.39 (1.03 – 1.88) [182]	2.06 (1.44 – 2.94) [101]	<0.001
Daily headache[b] (A)	16213 [124]	1 (reference) [32]	1.02 (0.65 – 1.62) [56]	1.88 (1.10 – 3.21) [36]	<0.001
Daily headache[b] (B)	16213 [124]	1 (reference) [32]	1.06 (0.66 – 1.68) [56]	1.97 (1.14 – 3.42) [36]	<0.001
Migraine diagnosis[c] (A)	15421 [563]	1 (reference) [126]	1.13 (0.91 – 1.42) [303]	1.32 (1.00 – 1.74) [134]	0.006
Migraine diagnosis[c] (B)	15421 [563]	1 (reference) [126]	1.12 (0.89 – 1.41) [303]	1.29 (0.98 – 1.71) [134]	0.072

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 16. Single-exposure ($IEM_{RC\text{-}hfa\_DECT}$) and two-exposure ($IEM_{RC\text{-}hfa\_DECT}$, texting) multivariable logistic regression models. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by RF-EMF dose (mJ/kg/week) to the brain of the participants at baseline ($IEM_{RC\text{-}hfa\_DECT}$) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

	RF-EMF dose (mJ/kg/week in categories[a])					
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	63933 [5201]	0.94 (0.87 – 1.01) [1376]	1 (reference) [2076]	1.06 (0.97 – 1.15) [1110]	1.11 (1.00 – 1.24) [639]	0.002
Weekly headache[b] (B)	63933 [5201]	0.99 (0.91 – 1.07) [1376]	1 (reference) [2076]	1.02 (0.94 – 1.11) [1110]	1.05 (0.95 – 1.17) [639]	0.284
Severe weekly headache[b] (A)	63350 [1578]	1.01 (0.89 – 1.14) [455]	1 (reference) [634]	1.10 (0.95 – 1.28) [310]	1.36 (1.09 – 1.61) [179]	0.008
Severe weekly headache[b] (B)	63350 [1578]	1.03 (0.90 – 1.17) [455]	1 (reference) [634]	1.07 (0.92 – 1.24) [310]	1.22 (1.00 – 1.49) [179]	0.110
Daily headache[b] (A)	63933 [362]	1.05 (0.79 – 1.40) [88]	1 (reference) [129]	0.98 (0.73 – 1.31) [80]	1.26 (0.91 – 1.75) [65]	0.399
Daily headache[b] (B)	63933 [362]	1.10 (0.82 – 1.48) [88]	1 (reference) [129]	0.93 (0.69 – 1.25) [80]	1.13 (0.81 – 1.58) [65]	0.973
Migraine diagnosis[c] (A)	51578 [1728]	0.97 (0.85 – 1.10) [392]	1 (reference) [687]	0.98 (0.86 – 1.12) [375]	1.21 (1.03 – 1.42) [274]	0.028
Migraine diagnosis[c] (B)	51578 [1728]	1.01 (0.88 – 1.16) [392]	1 (reference) [687]	0.95 (0.83 – 1.09) [375]	1.13 (0.96 – 1.33) [274]	0.369

[a]Very low: $IEM_{RC\text{-}hfa\_DECT} < 1449.0$ (mJ/kg/week); Low: $IEM_{RC\text{-}hfa\_DECT} \geq 1449.0$ & $IEM_{RC\text{-}hfa\_DECT} < 4196.1$ (mJ/kg/week); Medium: $IEM_{RC\text{-}hfa\_DECT} \geq 4196.1$ & $IEM_{RC\text{-}hfa\_DECT} < 7746.2$ (mJ/kg/week); High: $IEM_{RC\text{-}hfa\_DECT} \geq 7746.2$ (mJ/kg/week), (max=19047.05 mJ/kg/week).

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 17. Single-exposure (texting) and two-exposure ($IEM_{RC\text{-}hfa\_DECT}$, texting) multivariable logistic regression models. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline ($IEM_{RC\text{-}hfa\_DECT}$) without (A) and with (B) mutual adjustment for RF-EMF dose (mJ/kg/week) to the brain of the participants at baseline. Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	63933 [5201]	1 (reference) [2658]	1.18 (1.10 – 1.26) [1916]	1.41 (1.27 – 1.57) [627]	<0.001
Weekly headache[b] (B)	63933 [5201]	1 (reference) [2658]	1.17 (1.08 – 1.26) [1916]	1.39 (1.24 – 1.55) [627]	<0.001
Severe weekly headache[b] (A)	63350 [1578]	1 (reference) [837]	1.04 (0.92 – 1.18) [520]	1.58 (1.32 – 1.89) [221]	<0.001
Severe weekly headache[b] (B)	63350 [1578]	1 (reference) [837]	1.03 (0.91 – 1.18) [520]	1.53 (1.27 – 1.85) [221]	<0.001
Daily headache[b] (A)	63933 [362]	1 (reference) [171]	1.08 (0.83 – 1.41) [126]	1.77 (1.25 – 2.50) [65]	<0.001
Daily headache[b] (B)	63933 [362]	1 (reference) [171]	1.11 (0.84 – 1.47) [126]	1.78 (1.24 – 2.57) [65]	<0.001
Migraine diagnosis[c] (A)	51578 [1728]	1 (reference) [763]	1.11 (0.99 – 1.25) [687]	1.51 (1.28 – 1.78) [278]	<0.001
Migraine diagnosis[c] (B)	51578 [1728]	1 (reference) [763]	1.12 (0.99 – 1.27) [687]	1.49 (1.25 – 1.77) [278]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 18. Single-exposure (RC) and two-exposure (RC, texting) multivariable logistic regression models.
Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates (RC)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

		Amount of mobile phone use at baseline (call-time in categories[a])				
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.94 (0.87 – 1.01) [1388]	1 (reference) [2053]	1.08 (1.00 – 1.16) [1592]	1.12 (0.99 – 1.27) [419]	0.004
Weekly headache[b] (B)	66858 [5452]	0.99 (0.91 – 1.06) [1388]	1 (reference) [2053]	1.04 (0.97 – 1.12) [1592]	1.04 (0.92 – 1.18) [419]	0.348
Severe weekly headache[b] (A)	66234 [1660]	0.98 (0.86 – 1.11) [449]	1 (reference) [635]	1.16 (1.01 – 1.32) [445]	1.39 (1.20 – 1.85) [131]	0.001
Severe weekly headache[b] (B)	66234 [1660]	1.00 (0.87 – 1.14) [449]	1 (reference) [635]	1.12 (0.98 – 1.28) [445]	1.24 (1.07 – 1.68) [131]	0.021
Daily headache[b] (A)	66858 [382]	1.04 (0.79 – 1.39) [91]	1 (reference) [126]	1.04 (0.79 – 1.36) [120]	1.27 (0.94 – 1.98) [45]	0.315
Daily headache[b] (B)	66858 [382]	1.09 (0.81 – 1.46) [91]	1 (reference) [126]	0.98 (0.75 – 1.28) [120]	1.17 (0.80 – 1.71) [45]	0.787
Migraine diagnosis[c] (A)	53576 [1812]	0.93 (0.82 – 1.06) [384]	1 (reference) [690]	0.98 (0.87 – 1.11) [539]	1.27 (1.04 – 1.53) [199]	0.010
Migraine diagnosis[c] (B)	53576 [1812]	0.98 (0.85 – 1.12) [384]	1 (reference) [690]	0.95 (0.84 – 1.08) [539]	1.26 (1.00 – 1.49) [199]	0.140

[a]Very low: RC < 25.5 (min/week); Low: RC ≥ 25.5 & RC < 65.1 (min/week); Medium: RC ≥ 65.1 & RC < 113.5 (min/week); High: RC ≥ 113.5 (min/week), (max=270.3 min/week).
[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 19. Single-exposure (texting) and two-exposure (RC, texting) multivariable logistic regression models.
Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates (RC)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.17 (1.10 – 1.26) [2012]	1.42 (1.28 – 1.58) [670]	<0.001
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.16 (1.08 – 1.25) [2012]	1.40 (1.25 – 1.56) [670]	<0.001
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.06 (0.94 – 1.20) [553]	1.63 (1.37 – 1.94) [239]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.03 (0.91 – 1.18) [553]	1.53 (1.27 – 1.84) [239]	<0.001
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.08 (0.84 – 1.40) [131]	1.86 (1.33 – 2.61) [70]	<0.001
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.11 (0.84 – 1.46) [131]	1.86 (1.30 – 2.66) [70]	<0.001
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.12 (1.00 – 1.26) [727]	1.51 (1.29 – 1.78) [294]	<0.001
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.12 (0.99 – 1.26) [727]	1.46 (1.23 – 1.73) [294]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 20. Single-exposure (RC-hfa) and two-exposure (RC-hfa, texting) multivariable logistic regression models, excluding painkiller use. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

	Amount of mobile phone use at baseline (call-time in categories[a])					
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.94 (0.87 – 1.01) [1432]	1 (reference) [2160]	1.08 (0.99 – 1.17) [1086]	1.10 (1.00 – 1.22) [774]	0.002
Weekly headache[b] (B)	66858 [5452]	0.99 (0.91 – 1.06) [1432]	1 (reference) [2160]	1.04 (0.96 – 1.13) [1086]	1.04 (0.94 – 1.15) [774]	0.291
Severe weekly headache[b] (A)	66234 [1660]	0.96 (0.85 – 1.09) [465]	1 (reference) [671]	1.08 (0.93 – 1.25) [299]	1.36 (1.13 – 1.63) [225]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	0.99 (0.86 – 1.12) [465]	1 (reference) [671]	1.04 (0.90 – 1.21) [299]	1.25 (1.03 – 1.50) [225]	0.038
Daily headache[b] (A)	66858 [382]	1.03 (0.78 – 1.37) [94]	1 (reference) [136]	0.97 (0.73 – 1.30) [75]	1.22 (0.90 – 1.67) [77]	0.429
Daily headache[b] (B)	66858 [382]	1.08 (0.81 – 1.45) [94]	1 (reference) [136]	0.92 (0.69 – 1.24) [75]	1.09 (0.79 – 1.49) [77]	0.901
Migraine diagnosis[c] (A)	53576 [1812]	0.92 (0.81 – 1.05) [396]	1 (reference) [725]	0.97 (0.85 – 1.11) [355]	1.19 (1.02 – 1.39) [336]	0.010
Migraine diagnosis[c] (B)	53576 [1812]	0.96 (0.84 – 1.10) [396]	1 (reference) [725]	0.94 (0.82 – 1.08) [355]	1.11 (0.96 – 1.30) [336]	0.226

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 21. Single-exposure (texting) and two-exposure (RC-hfa, texting) multivariable logistic regression models, excluding painkiller use. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.18 (1.10 – 1.26) [2012]	1.43 (1.29 – 1.59) [670]	<0.001
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.16 (1.08 – 1.25) [2012]	1.41 (1.26 – 1.57) [670]	<0.001
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.07 (0.94 – 1.20) [553]	1.65 (1.39 – 1.97) [239]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.05 (0.92 – 1.19) [553]	1.58 (1.31 – 1.90) [239]	<0.001
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.09 (0.84 – 1.41) [131]	1.89 (1.35 – 2.65) [70]	<0.001
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.12 (0.86 – 1.48) [131]	1.92 (1.35 – 2.74) [70]	<0.001
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.13 (1.01 – 1.27) [727]	1.53 (1.30 – 1.80) [294]	<0.001
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.12 (0.99 – 1.26) [727]	1.49 (1.26 – 1.77) [294]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 22. Single-exposure (RC-hfa) and two-exposure (RC-hfa, texting) multivariable logistic regression models with minimal adjustment for sex, age group, country. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

		Amount of mobile phone use at baseline (call-time in categories[a])				
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.95 (0.89 – 1.02) [1432]	1 (reference) [2160]	1.09 (1.01 – 1.18) [1086]	1.16 (1.05 – 1.28) [774]	<0.001
Weekly headache[b] (B)	66858 [5452]	1.00 (0.93 – 1.08) [1432]	1 (reference) [2160]	1.05 (0.97 – 1.14) [1086]	1.08 (0.97 – 1.19) [774]	0.164
Severe weekly headache[b] (A)	66234 [1660]	0.99 (0.88 – 1.12) [465]	1 (reference) [671]	1.10 (0.95 – 1.27) [299]	1.45 (1.21 – 1.74) [225]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1.02 (0.89 – 1.16) [465]	1 (reference) [671]	1.06 (0.92 – 1.22) [299]	1.30 (1.08 – 1.56) [225]	0.023
Daily headache[b] (A)	66858 [382]	1.08 (0.82 – 1.42) [94]	1 (reference) [136]	0.99 (0.74 – 1.33) [75]	1.33 (0.97 – 1.81) [77]	0.310
Daily headache[b] (B)	66858 [382]	1.14 (0.86 – 1.52) [94]	1 (reference) [136]	0.94 (0.70 – 1.26) [75]	1.15 (0.84 – 1.58) [77]	0.946
Migraine diagnosis[c] (A)	53576 [1812]	0.93 (0.82 – 1.06) [396]	1 (reference) [725]	0.98 (0.85 – 1.12) [355]	1.23 (1.06 – 1.43) [336]	0.004
Migraine diagnosis[c] (B)	53576 [1812]	0.97 (0.85 – 1.11) [396]	1 (reference) [725]	0.95 (0.83 – 1.08) [355]	1.14 (0.98 – 1.33) [336]	0.175

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).
[b]Adjusted for sex, age group, and country at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, and country at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 23. Single-exposure (texting) and two-exposure (RC-hfa, texting) multivariable logistic regression models with minimal adjustment for sex, age group, country. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.18 (1.10 – 1.26) [2012]	1.57 (1.41 – 1.74) [670]	<0.001
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.17 (1.08 – 1.25) [2012]	1.53 (1.38 – 1.71) [670]	<0.001
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.05 (0.93 – 1.19) [553]	1.85 (1.56 – 2.20) [239]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.04 (0.92 – 1.19) [553]	1.76 (1.47 – 2.11) [239]	<0.001
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.07 (0.83 – 1.38) [131]	2.14 (1.54 – 2.98) [70]	<0.001
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.12 (0.85 – 1.46) [131]	2.17 (1.53 – 3.08) [70]	<0.001
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.12 (1.00 – 1.26) [727]	1.60 (1.36 – 1.88) [294]	<0.001
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.11 (0.99 – 1.26) [727]	1.55 (1.31 – 1.84) [294]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.
[b]Adjusted for sex, age group, and country at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.
[c]Adjusted for sex, age group, and country at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 24. Single-exposure (RC-hfa) and two-exposure (RC-hfa, texting) multivariable logistic regression models ("high" call-time exposure category 80th percentile). Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

		Amount of mobile phone use at baseline (call-time in categories[a])				
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.94 (0.88 – 1.02) [1432]	1 (reference) [2160]	1.03 (0.93 – 1.15) [511]	1.11 (1.03 – 1.20) [1349]	0.001
Weekly headache[b] (B)	66858 [5452]	0.99 (0.92 – 1.07) [1432]	1 (reference) [2160]	1.01 (0.90 – 1.12) [511]	1.06 (0.98 – 1.15) [1349]	0.208
Severe weekly headache[b] (A)	66234 [1660]	0.98 (0.86 – 1.11) [465]	1 (reference) [671]	1.02 (0.83 – 1.25) [126]	1.20 (1.05 – 1.38) [398]	0.021
Severe weekly headache[b] (B)	66234 [1660]	1.00 (0.88 – 1.14) [465]	1 (reference) [671]	1.00 (0.82 – 1.23) [126]	1.14 (0.99 – 1.31) [398]	0.184
Daily headache[b] (A)	66858 [382]	1.05 (0.80 – 1.39) [94]	1 (reference) [136]	1.03 (0.72 – 1.47) [44]	1.10 (0.84 – 1.44) [108]	0.790
Daily headache[b] (B)	66858 [382]	1.10 (0.82 – 1.47) [94]	1 (reference) [136]	0.99 (0.69 – 1.42) [44]	0.99 (0.75 – 1.31) [108]	0.598
Migraine diagnosis[c] (A)	53576 [1812]	0.94 (0.82 – 1.06) [396]	1 (reference) [725]	1.00 (0.84 – 1.19) [190]	1.07 (0.95 – 1.22) [501]	0.122
Migraine diagnosis[c] (B)	53576 [1812]	0.98 (0.86 – 1.12) [396]	1 (reference) [725]	0.98 (0.82 – 1.16) [190]	1.02 (0.89 – 1.16) [501]	0.735

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 62.8 (min/week); High: RC-hfa ≥ 62.8 (min/week), (max=256.8 min/week).

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 25. Single-exposure (texting) and two-exposure (RC-hfa, texting) multivariable logistic regression models ("high" call-time exposure category 80th percentile). Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.17 (1.10 – 1.26) [2012]	1.42 (1.28 – 1.58) [670]	<0.001
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.16 (1.08 – 1.25) [2012]	1.39 (1.25 – 1.55) [670]	<0.001
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.06 (0.94 – 1.20) [553]	1.63 (1.37 – 1.94) [239]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.04 (0.91 – 1.18) [553]	1.57 (1.30 – 1.88) [239]	<0.001
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.08 (0.84 – 1.40) [131]	1.86 (1.33 – 2.61) [70]	<0.001
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.12 (0.85 – 1.47) [131]	1.92 (1.35 – 2.73) [70]	<0.001
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.21 (1.00 – 1.26) [727]	1.51 (1.29 – 1.78) [294]	<0.001
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.11 (0.99 – 1.26) [727]	1.49 (1.26 – 1.77) [294]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 26. Single-exposure (RC-hfa) and two-exposure (RC-hfa, texting) multivariable logistic regression models, with RF-hfa exposure categorised into quartiles. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Number of participants with the outcome indicated in square brackets.

	Amount of mobile phone use at baseline (call-time in categories[a])					
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	0.94 (0.87 – 1.03) [918]	1 (reference) [1614]	1.04 (0.95 – 1.13) [1571]	1.13 (1.04 – 1.24) [1349]	0.001
Weekly headache[b] (B)	66858 [5452]	0.98 (0.90 – 1.08) [918]	1 (reference) [1614]	1.01 (0.93 – 1.10) [1571]	1.07 (0.97 – 1.17) [1349]	0.165
Severe weekly headache[b] (A)	66234 [1660]	1.12 (0.97 – 1.29) [318]	1 (reference) [503]	1.15 (1.00 – 1.33) [441]	1.32 (1.13 – 1.54) [398]	0.025
Severe weekly headache[b] (B)	66234 [1660]	1.14 (0.98 – 1.33) [318]	1 (reference) [503]	1.14 (0.98 – 1.32) [441]	1.24 (1.06 – 1.46) [398]	0.227
Daily headache[b] (A)	66858 [382]	1.06 (0.75 – 1.48) [59]	1 (reference) [85]	1.21 (0.88 – 1.65) [130]	1.23 (0.88 – 1.71) [108]	0.313
Daily headache[b] (B)	66858 [382]	1.09 (0.77 – 1.54) [59]	1 (reference) [85]	1.19 (0.87 – 1.63) [130]	1.11 (0.79 – 1.56) [108]	0.729
Migraine diagnosis[c] (A)	53576 [1812]	0.94 (0.81 – 1.10) [244]	1 (reference) [516]	0.94 (0.81 – 1.08) [551]	1.04 (0.90 – 1.20) [501]	0.248
Migraine diagnosis[c] (B)	53576 [1812]	0.99 (0.85 – 1.17) [244]	1 (reference) [516]	0.91 (0.79 – 1.05) [551]	0.97 (0.83 – 1.12) [501]	0.580

[a]Very low: RC-hfa < 11.8 (min/week); Low: RC-hfa ≥ 11.8 & RC-hfa < 30.0 (min/week); Medium: RC-hfa ≥ 30.0 & RC-hfa < 61.9 (min/week); High: RC-hfa ≥ 61.9 (min/week), (max=256.8 min/week).

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 27. Single-exposure (texting) and two-exposure (RC-hfa, texting) multivariable logistic regression models, with RF-hfa exposure categorised into quartiles. Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	66858 [5452]	1 (reference) [2770]	1.17 (1.10 – 1.26) [2012]	1.42 (1.28 – 1.58) [670]	<0.001
Weekly headache[b] (B)	66858 [5452]	1 (reference) [2770]	1.16 (1.07 – 1.24) [2012]	1.39 (1.25 – 1.55) [670]	<0.001
Severe weekly headache[b] (A)	66234 [1660]	1 (reference) [868]	1.06 (0.94 – 1.20) [553]	1.63 (1.37 – 1.94) [239]	<0.001
Severe weekly headache[b] (B)	66234 [1660]	1 (reference) [868]	1.05 (0.92 – 1.19) [553]	1.58 (1.31 – 1.90) [239]	<0.001
Daily headache[b] (A)	66858 [382]	1 (reference) [181]	1.08 (0.84 – 1.40) [131]	1.86 (1.33 – 2.61) [70]	<0.001
Daily headache[b] (B)	66858 [382]	1 (reference) [181]	1.07 (0.81 – 1.40) [131]	1.85 (1.30 – 2.63) [70]	<0.001
Migraine diagnosis[c] (A)	53576 [1812]	1 (reference) [791]	1.21 (1.00 – 1.26) [727]	1.51 (1.29 – 1.78) [294]	<0.001
Migraine diagnosis[c] (B)	53576 [1812]	1 (reference) [791]	1.14 (1.01 – 1.29) [727]	1.52 (1.28 – 1.80) [294]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 28. Single-exposure (RC-hfa) and two-exposure (RC-hfa, texting) multivariable logistic regression models (complete-case analysis). Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)) without (A) and with (B) mutual adjustment for the number of text messages sent with a mobile phone at baseline. Complete-case analysis. Number of participants with the outcome indicated in square brackets.

	Amount of mobile phone use at baseline (call-time in categories[a])					
	No. of participants	**Very low**	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	58229 [4803]	0.95 (0.88 – 1.03) [1243]	1 (reference) [1953]	1.08 (0.99 – 1.17) [966]	1.08 (0.97 – 1.20) [641]	0.021
Weekly headache[b] (B)	58229 [4803]	1.00 (0.92 – 1.08) [1243]	1 (reference) [1953]	1.05 (0.96 – 1.14) [966]	1.02 (0.92 – 1.14) [641]	0.593
Severe weekly headache[b] (A)	57679 [1457]	0.97 (0.85 – 1.11) [408]	1 (reference) [611]	1.07 (0.92 – 1.25) [262]	1.31 (1.07 – 1.61) [176]	0.007
Severe weekly headache[b] (B)	57679 [1457]	0.99 (0.86 – 1.13) [408]	1 (reference) [611]	1.04 (0.88 – 1.21) [262]	1.22 (0.99 – 1.50) [176]	0.080
Daily headache[b] (A)	58229 [312]	1.03 (0.76 – 1.39) [74]	1 (reference) [118]	0.95 (0.69 – 1.30) [63]	1.08 (0.77 – 1.54) [57]	0.868
Daily headache[b] (B)	58229 [312]	1.09 (0.80 – 1.50) [74]	1 (reference) [118]	0.90 (0.65 – 1.23) [63]	0.96 (0.67 – 1.37) [57]	0.493
Migraine diagnosis[c] (A)	49783 [1648]	0.93 (0.81 – 1.06) [377]	1 (reference) [676]	0.97 (0.84 – 1.12) [318]	1.17 (0.99 – 1.38) [277]	0.030
Migraine diagnosis[c] (B)	49783 [1648]	0.97 (0.84 – 1.11) [377]	1 (reference) [676]	0.94 (0.82 – 1.09) [318]	1.10 (0.93 – 1.30) [277]	0.362

[a]Very low: RC-hfa < 19.1 (min/week); Low: RC-hfa ≥ 19.1 & RC-hfa < 58.6 (min/week); Medium: RC-hfa ≥ 58.6 & RC-hfa < 107.8 (min/week); High: RC-hfa ≥ 107.8 (min/week), (max=256.8 min/week).

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

Supplementary Table 29. Single-exposure (texting) and two-exposure (RC-hfa, texting) multivariable logistic regression models (complete-case analysis). Odds ratio (OR) with 95% CI for weekly headache, severe weekly headache, daily headache, and migraine diagnosis at follow-up by number of text messages sent with a mobile phone at baseline without (A) and with (B) mutual adjustment for the amount of mobile phone use at baseline (weekly minutes of call-time, country-specific regression calibrated estimates adjusted by the proportion of hands-free use (RC-hfa)). Complete-case analysis. Number of participants with the outcome indicated in square brackets.

	Number of text messages sent with a mobile phone at baseline (frequency of texting in categories[a])				
	No. of participants	**Low**	**Medium**	**High**	**P trend**
Weekly headache[b] (A)	58229 [4803]	1 (reference) [2427]	1.16 (1.08 – 1.25) [1802]	1.41 (1.26 – 1.57) [574]	<0.001
Weekly headache[b] (B)	58229 [4803]	1 (reference) [2427]	1.15 (1.07 – 1.24) [1802]	1.39 (1.24 – 1.56) [574]	<0.001
Severe weekly headache[b] (A)	57679 [1457]	1 (reference) [771]	1.04 (0.92 – 1.19) [491]	1.56 (1.29 – 1.89) [195]	<0.001
Severe weekly headache[b] (B)	57679 [1457]	1 (reference) [771]	1.03 (0.90 – 1.18) [491]	1.50 (1.23 – 1.83) [195]	<0.001
Daily headache[b] (A)	58229 [312]	1 (reference) [144]	1.12 (0.85 – 1.48) [113]	1.86 (1.28 – 2.70) [55]	<0.001
Daily headache[b] (B)	58229 [312]	1 (reference) [144]	1.17 (0.87 – 1.58) [113]	1.95 (1.31 – 2.88) [55]	<0.001
Migraine diagnosis[c] (A)	49783 [1648]	1 (reference) [744]	1.12 (1.00 – 1.26) [657]	1.47 (1.24 – 1.75) [247]	<0.001
Migraine diagnosis[c] (B)	49783 [1648]	1 (reference) [744]	1.11 (0.98 – 1.26) [657]	1.44 (1.20 – 1.72) [247]	<0.001

[a]Low: Never/Less than 1 text message per week/1-6 text messages per week; Medium: 1-9 text messages per day; High: 10-29 text messages per day/30 or more text messages per day.

[b]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with (weekly, severe weekly, daily) headache at baseline.

[c]Adjusted for sex, age group, country, highest level of education attained, BMI group, general health indicator, sleep disturbance index, painkiller use, depression diagnosis, high blood pressure diagnosis, smoking status, and alcohol consumption at baseline. Excluding participants with migraine diagnosis at baseline.

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$$Q = \begin{pmatrix} q_{11} & q_{12} & q_{13} & q_{14} \\ q_{21} & q_{22} & q_{23} & q_{24} \\ q_{31} & q_{32} & q_{33} & q_{34} \\ q_{41} & q_{42} & q_{43} & q_{44} \end{pmatrix}$$

Chapter 3: Time course of health complaints attributed to RF-EMF exposure and predictors of electromagnetic hypersensitivity over 10 years in a prospective cohort of Dutch adults

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Abstract

Background: Some individuals attribute health complaints to radiofrequency electromagnetic field (RF-EMF) exposure. This condition, known as idiopathic environmental intolerance attributed to RF-EMFs (IEI-RF) or electromagnetic hypersensitivity (EHS), can be disabling for those who are affected. In this study we assessed factors related to developing, maintaining, or discarding IEI-RF over the course of 10 years, and predictors of developing EHS at follow-up using a targeted question without the condition of reporting health complaints attributed to RF-EMF exposure.

Methods: Participants (n=892, mean age 50 at baseline, 52 % women) from the Dutch Occupational and Environmental Health Cohort Study AMIGO filled in questionnaires in 2011/2012 (T_0), 2013 (T_1), and 2021 (T_4) where information pertaining to perceived RF-EMF exposure and risk, non-specific symptoms, sleep problems, IEI-RF, and EHS was collected. We fitted multi-state Markov models to represent how individuals transitioned between states ("yes", "no") of IEI-RF.

Results: At each time point, about 1 % of study participants reported health complaints that they attributed to RF-EMF exposure. While this percentage remained stable, the individuals who reported such complaints changed over time: of nine persons reporting health complaints at T_0, only one reported IEI-RF at both T_1 and T_4, and two newly reported health complaints at T_4. Overall, participants had a 95 % chance of transitioning from "yes" to "no" over a time course of 10 years, and a chance of 1 % of transitioning from "no" to "yes". Participants with high perceived RF-EMF exposure and risk had a general tendency to move more frequently between states.

Conclusions: We observed a low prevalence of IEI-RF in our population. Prevalence did not vary strongly over time but there was a strong aspect of change: over 10 years, there was a high probability of not attributing symptoms to RF-EMF exposure anymore. IEI-RF appears to be a more transient condition than previously assumed.

Introduction

Over the past few decades, the rapid advancement of wireless technologies and electronic devices has led to a considerable increase in exposure to radiofrequency electromagnetic fields (RF-EMFs) and RF signals are now part of everyday life. The condition known as idiopathic environmental intolerance attributed to electromagnetic fields (IEI-EMF) is used to describe individuals who attribute health complaints such as headaches, sleep disturbances, or problems in concentrating, to EMF exposure (Baliatsas et al., 2012; Martens et al., 2017; Röösli et al., 2004), and in severe cases it can be disabling or result in a lower quality of life (Kjellqvist et al., 2016). Similarly, the term electromagnetic hypersensitivity (EHS) refers to someone who claims to be hypersensitive to EMFs, but does not necessarily report health complaints attributed to such exposure (Röösli et al., 2010). In particular, IEI-EMF and EHS have been hypothesized to correspond to different levels of involvement in the EMF topic (Röösli et al., 2010). Nevertheless, diagnostic criteria for these conditions are not fully established and research has yet to produce clear evidence on the mechanisms causing people to attribute health complaints to EMF exposure or to define themselves as hypersensitive to EMFs (Baliatsas et al., 2009; Dieudonné, 2019, 2020; Stein & Udasin, 2020), although psychosocial factors are thought to play a role (Augner & Hacker, 2009; Baliatsas et al., 2015; Frick et al., 2002; Martens et al., 2018; Ramirez-Vazquez et al., 2019; Rubin et al., 2010; Watrin et al., 2022). As a consequence, the terms IEI-EMF and EHS are frequently used interchangeably in epidemiological studies, and this is likely to affect the range in estimated prevalence, which in industrialized countries varies between 1.5 % and 21 % (Eltiti et al., 2007; Hillert et al., 2002; Karvala et al., 2018; Levallois et al., 2002; Schreier et al., 2006).

Little is understood in how far IEI-EMF changes over time: intriguingly, some studies observed a similar percentage of IEI-EMF at baseline and at follow-up one or two years later (Kowall et al., 2012; Martens et al., 2018; Röösli et al., 2010), despite a high turnover rate in the population reporting IEI-EMF at follow-up. This implies that attribution of health complaints to EMF exposure is temporary for many but not all people. Therefore, it would be informative to study not only predictors of developing IEI-EMF, but also predictors of maintaining or discarding IEI-EMF. This requires a longitudinal design with repeat surveys on both symptom experience and attribution to EMF exposure, to understand what comes first. To the best of our knowledge, while several studies have addressed risk factors for developing IEI-EMF, few research efforts have targeted the question for whom IEI-EMF is a transient phenomenon.

In this study we aim to evaluate the time course of attribution of health complaints specifically to RF-EMF exposure (IEI-RF) in a Dutch population assessed at three time points over the course of 10 years by examining factors that are related to developing, maintaining, or discarding IEI-RF, defined as reporting any health complaint attributed to RF-EMF exposure sources. Second, we aim to assess predictors of developing EHS at

follow-up using a question targeting the notion of being electromagnetic hypersensitive, without the condition of self-reporting health complaints attributed to RF-EMF exposure.

Material and methods

Study participants

We used data from the population-based occupational and environmental health prospective cohort study (AMIGO) established in 2011/2012 to investigate environmental and occupational determinants of diseases and symptoms in the Dutch adult population. The rationale, study design and participant recruitment in AMIGO were described in detail previously (Slottje et al., 2014). In short, AMIGO participants were recruited from the general population in the Netherlands through the Primary Care Database of the Netherlands Institute for Health Services Research (NIVEL), which consists of routinely recorded data from health care providers to monitor health and utilization of health services in the Dutch population (*Nivel Primary Care Database | Nivel*, 2022). The sample includes 14,829 adults (16 % of those invited), aged 31-65 years at the time of data collection (2011/2012), who were randomly selected within households based on their address. The AMIGO cohort study includes dedicated questionnaires to assess relationships between exposure, risk perception, symptom reporting and symptom attribution to environmental factors including RF-EMFs. Participants filled in an online questionnaire at baseline (2011/2012; T_0) and in 2015 (n=7,905; T_3; response rate 54 %), and a targeted subset of participants sampled based on contrast in perceived and estimated RF-EMF exposure at baseline filled in two additional follow-up questionnaires in 2013 (n=2,228; T_1; response rate 56 %) and 2014 (n=1,740; T_2; response rate 78 %) to answer questions about perceived RF-EMF and other environmental factor exposure and risk, health concerns, symptom attribution to RF-EMF exposure, non-specific symptoms and sleep disturbances (Martens et al., 2017, 2018). We performed an update in 2021 (T_4) in which individuals who had participated at T_1 completed a questionnaire where information pertaining to RF-EMF perceptions (perceived exposure, risk and concern, including pertaining to 5G technology), symptoms, and attribution to RF-EMF exposure were assessed again (n=892; response rate 40 %). In the 2021 (T_4) questionnaire additional items were added related to EHS. We included in the current analyses participants who filled in questionnaires at time points T_0, T_1, and T_4 in order to achieve the largest possible sample size (Figure 1).

Health complaints attributed to RF-EMF exposure – IEI-RF

Self-reported health complaints attributed to RF-EMF exposure (IEI-RF) were assessed at time points T_0 and T_1 with the subsequent questions: “Do you currently have health complaints that you attribute to the environment” and “if so, to what environmental

factors/sources, select from the following or describe another factor/source". From this list of sources we selected: (1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones; (3) electromagnetic fields from cordless phones; (possible answers "yes" or "no")?", and at time point T_4 with the subsequent questions: "Do you currently have health complaints that you attribute to the environment" and "if so, to what environmental factors/sources, select from the following or describe another factor/source". From this list of sources we selected: (1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones, cordless phones and other wireless devices, (e.g. laptop, tablet); (3) electromagnetic fields from 5G technology; (possible answers "yes" or "no")?". Participants were considered as IEI-RF at any time point if at least one RF-EMF category was marked in the respective questionnaires.

Self-reported notion of being electromagnetic hypersensitive – EHS

At T_4 we asked participants to indicate to which extent they considered themselves as electromagnetic hypersensitive by asking the following question: "Do you think you are electromagnetic hypersensitive (on a scale of 0-6, where 0=not at all and 6=very much)?". In the analyses we classified as electromagnetic hypersensitive participants whose score ranged between 4 and 6.

Perceived RF-EMF exposure and risk

Perceived exposure to RF-EMFs (among other environmental exposures) was assessed at T_0 and T_1 with the question: "To what extent do you think you are exposed to: (1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones; (3) electromagnetic fields from cordless phones; (on a scale of 0-6, where 0=not at all and 6=very much)?", and at time point T_4 with the question: "To what extent do you think you are exposed to: (1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones, cordless phones and other wireless devices, (e.g. laptop, tablet); (3) electromagnetic fields from 5G technology; (on a scale of 0-6, where 0=not at all and 6=very much)?".
Perceived risk with respect to RF-EMFs (amongst other specified environmental factors) was assessed at T_0 and T_1 with the question: "To what extent do you think that ((1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones; (3) electromagnetic fields from cordless phones) pose a risk to the health in everyday circumstances? (on a scale of 0-6, where 0=not at all and 6=very much)", and at time point T_4 with the question: "To what extent do you think that ((1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones, cordless phones and other wireless devices, (e.g. laptop, tablet); (3) electromagnetic fields from 5G technology) pose a risk to the health in everyday circumstances? (on a scale of 0-6, where 0=not at all and 6=very much)".

The cut-offs to define low/high exposure and risk perception categories were calculated based on the distribution of perceived RF-EMF exposure and risk at T_0 (low: 0^{th}-90^{th} percentile, high: 90^{th}-100^{th} percentile, cut-off point $_{\text{perceived RF-EMF exposure}}$=12; cut-off point $_{\text{perceived RF-EMF risk}}$=12).

Self-reported non-specific symptoms and sleep disturbances

We assessed non-specific symptoms and sleep disturbances at time points T_0, T_1, and T_4. For the first, we used the Four-Dimensional Symptom Questionnaire (4DSQ) (Terluin et al., 2006), a self-report questionnaire developed in the Dutch language and validated to discriminate in clinical practice between four dimensions (distress, somatization, anxiety, depression). We calculated the total symptom score (range 0-32) from the somatization scale (4DSQ-S) which consists of 16 nonspecific somatic symptoms (e.g. headache, palpitations, low back pain) commonly reported by patients with somatization (disorder). Participants self-reported on a 5-point scale ranging from "no" to "constantly" whether they had experienced any of these symptoms during the previous week. To obtain a total score, we trichotomized and then summed over the symptoms (no=0; sometimes=1; regularly/often/constantly=2) (Martens et al., 2017). Sleep disturbances were assessed using the 6-item medical outcomes study (MOS) scale, a sleep problem index which ranges from 0 to 100, with higher scores indicating more sleep disturbances or lower sleep quality (Spritzer & Hays, 2003).

Socio-demographic characteristics

Socio-demographic characteristics collected at baseline included sex, age, the highest level of education attained (low: primary school, lower vocational training or lower secondary education; intermediate: intermediate vocational education or intermediate/higher secondary education; high: higher vocational education or university degree), and self-reported mobile phone use (user; nonuser). In addition, urbanicity level was determined for each participants home address based on the density of addresses (very highly urban: ≥ 2,500 addresses per km^2; highly urban: 1,500–2,500 addresses per km^2; moderately urban: 1,000–1,500 addresses per km^2; little urban: 500–1,000 addresses per km^2; non-urban: < 500 addresses per km^2) (Statistiek, 2011).

Statistical analysis

We calculated descriptive statistics for age, sex, the highest level of education attained, urbanicity level, and self-reported mobile phone use at baseline, and at each time point for perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, and MOS sleep index. We used one-way repeated measures ANOVA to compare group means of 4DSQ-S score and MOS sleep index, respectively, across all time points. The proportion of participants reporting IEI-RF was calculated at each time point T_0, T_1, and T_4, whereas the

proportion of those defining themselves as EHS was only available at T_4.

We used the R package *msm* to calculate the observed transitions and transition probabilities of IEI-RF over different time intervals, and fit multi-state Markov models to our data (Jackson, 2011). In short, the multi-state Markov model is a flexible way of describing a process in which an individual moves through a discrete set of states, assuming that there is a continuous process underlying the data (i.e. the event varies continuously through time, but is only observed at the same times as the state of the Markov process). It relies on the Markov assumption that future evolution only depends on the current state (Kalbfleisch & Lawless, 1985). We fitted multi-state Markov models to represent how individuals in our cohort transitioned between two states defined by the presence ("yes") or absence ("no") of IEI-RF. More specifically, we estimated four multi-state Markov models including perceived RF-EMF exposure (Model 1), perceived RF-EMF risk (Model 2), 4DSQ-S score (Model 3), MOS sleep index (Model 4) as time-dependent risk factors to investigate potential time-variant effects on transition rates, adjusted for sex and age. To fit a multi-state model to our data, we estimated a transition intensity matrix in which each individual may transition from one state to another at each time point T_0, T_1, and T_4, and the next state to which the individual moves, and the time of the change, are governed by a set of transition intensities for each pair of states. The defined multi-state model is illustrated in Supplementary Figure 1. The intensities represent the instantaneous risk of moving from one state to another. It may depend on the time of the process, or more generally a set of individual-specific or time-varying explanatory variables, assuming that they are constant in between the observation times of the Markov process. We performed Pearson-type goodness-of-fit tests to assess the overall fit of the models (Titman & Sharples, 2008). This method, available in the *msm* package, compares observed and expected numbers of transitions between pairs of states for a series of transition starting times, transition time intervals and covariate categories, and it is intended for data which represent observations of the process at arbitrary times. In cases where there are several low expected counts in the resulting contingency tables, the number of observation time, time interval, or covariate categories may be reduced to improve the χ^2 approximation (Aguirre-Hernández & Farewell, 2002; Jackson, 2011).

We explored the association between EHS at T_4 and perceived RF-EMF exposure and risk, 4DSQ-S score, MOS sleep index assessed at T_0. We estimated four logistic regression models including perceived RF-EMF exposure (Model 5), perceived RF-EMF risk (Model 6), 4DSQ-S score (Model 7), MOS sleep index (Model 8) as independent variables, adjusted for sex and age. We fitted two mutually adjusted logistic regression models where perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, and MOS sleep index were considered simultaneously, adjusted for sex and age (Model 9), and sex, age, the

highest level of education attained, urbanicity level, and self-reported mobile phone use (Model 10) as sensitivity analysis, respectively.
In addition, we conducted the following secondary analyses to explore the association between EHS at T_4 and perceived RF-EMF exposure and risk, 4DSQ-S score, MOS sleep index assessed at T_1: we estimated four logistic regression models including perceived RF-EMF exposure (Model 11), perceived RF-EMF risk (Model 12), 4DSQ-S score (Model 13), MOS sleep index (Model 14) as independent variables, adjusted for sex and age. We fitted two mutually adjusted logistic regression models where perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, and MOS sleep index were considered simultaneously, adjusted for sex and age (Model 15), and sex, age, the highest level of education attained, urbanicity level, and self-reported mobile phone use (Model 16) as sensitivity analysis, respectively.

This population-based cohort study was conducted according to an analysis plan developed a priori and defining in detail the planned statistical analysis (Supplementary Analysis Plan). Missing values (<1.0 %) were replaced with the most common category (categorical variables) or with the mean value (continuous variables). All analyses were conducted with the R statistical software, version 4.0.4. Computing code related to all analyses presented is publicly available at https://github.com/eugeniotraini/multistate_RF_EMF.

Results

Descriptive statistics

Baseline characteristics of the study population are presented in Table 1. The AMIGO sub-cohort for this analysis consisted of 892 adults, half of whom were male, with a mean age of 50 years. More than half of the respondents attained a high level of education and most of the participants lived in urban areas. Three-quarters of the cohort were mobile phone users.
Participant characteristics in the full cohort at baseline were similar to those of the respondents included in the sub-cohort, although highly educated participants and those living in urban areas were slightly overrepresented in the sub-cohort compared to the full cohort (Supplementary Table 1).
Median perception of RF-EMF exposure (T_0=5; T_1=6; T_4=9) and risk (T_0=4; T_1=6; T_4=9) showed a rising trend over time (Supplementary Figure 2), with around 5 % and 7 % of participants classified in the high perception group at T_0, values that increased up to 20 % and 14 % at T_4 (Table 2). The distribution of scores of perceived RF-EMF exposure and risk grouped by exposure source are presented in Supplementary Figure 3 and showed that participants at T_4 indicated they perceived themselves to be stronger exposed to and more at risk from RF-EMFs compared to T_0 and T_1. Additionally, around 28% of re-

spondents self-reported they were exposed to RF-EMFs from 5G at T_4, and the same percentage also applied to those who indicated that 5G may pose risks to their health. The 4DSQ-S score ($F(2,24)=1.39$, $p=0.3$) and MOS sleep index ($F(2,46)=1.62$, $p=0.2$) were not statistically significantly different at T_0, T_1, and T_4, respectively (Table 2).
Table 3 lists the proportion of participants reporting IEI-RF at each time point, and those self-declaring as EHS at T_4. Results showed that 12 % of the respondents claimed to be EHS at T_4, whereas the percentage of individuals reporting IEI-RF was limited in our population and did not vary substantially over time (ranging from 1.0 % at T_0 to 1.2 % at T_4) (Table 3).

Observed transitions, estimated transition probabilities, and multi-state Markov models

The observed transitions, that is the number of times each pair of states were observed in successive observation times between T_0 and T_1, T_1 and T_4, and any consecutive time points T_0, T_1, T_4, are shown in Supplementary Table 2. Results indicated that the number of participants transitioning between the two states of IEI-RF (from "no" to "yes", or "yes" to "no") between T_0 and T_1 (A) and T_1 and T_4 (B) was stable over time, however, the transition did not always involve the same participants. Of nine respondents reporting IEI-RF at T_0, three still reported the same at T_4, but only one of them also reported the same at both T_1 and T_4 (Supplementary Figure 4). Based on the results from the fitted transition probability matrix, we observed that participants had a 95 % chance of transitioning from "yes" to "no" over a time course of 10 years (46 % in 2 years' time), and a 1 % chance of transitioning from "no" to "yes" (0.6 % in 2 years' time) (Supplementary Table 3).
The results of the multi-state Markov models are presented in Table 4 and suggested that participants with a high perception of both RF-EMF exposure (Model 1) and risk (Model 2) at any time point had an increased tendency to switch state by attributing health complaints to RF-EMF exposure (HR=4.11, 95 % CI:0.87,19.53; HR=3.81, 95 % CI:0.76,19.18). On the other hand, participants had a reduced tendency of no longer attributing health complaints to RF-EMF exposure (HR=0.56, 95 % CI:0.11,2.82; HR=0.46, 95 % CI:0.10,2.16) compared to those in the low exposure perception group. 4DSQ-S score (Model 3), and MOS sleep index (Model 4) were not associated with transitioning between states.

Factors associated with the self-reported notion of being EHS

In Table 5 we present results from logistic regression on the association between the self-reported notion of being EHS at T_4 and independent variables assessed at T_0. In the models evaluating each independent variable separately, perceived RF-EMF exposure and risk, 4DSQ-S score, and MOS sleep index were significantly associated with

increased odds of being EHS at T_4. More specifically, participants who showed a high perception of RF-EMF exposure at T_0 had an increased odds of being EHS at T_4 (OR=4.17, 95 % CI:2.10,8.00). Similarly, participants with a high perception of RF-EMF risk at T_0 had an increased odds of being EHS at T_4 (OR=4.08, 95 % CI:2.26,7.17). Finally, both the 4DSQ-S score and the MOS sleep index at T_0 were associated with an increase in the odds of being EHS at T_4 (OR=1.07, 95 % CI:1.03,1.10; OR=1.02, 95 % CI:1.00,1.03). Results from the mutually adjusted model with minimal adjustment (Model 9) and full adjustment (Model 10) were consistent with those from the models evaluating each independent variable separately, although the estimates were generally attenuated (Table 5). Results from secondary analyses exploring the association between EHS at T_4 and perceived RF-EMF exposure and risk, 4DSQ-S score, MOS sleep index assessed at T_1 showed no discrepancies from the main results (Table 6).

Discussion

In our study we observed a low prevalence (~1 %) of adults reporting IEI-RF over the 10-year follow-up. While this 1 % of persons remained stable at all time points in our study, the individuals who reported IEI-RF changed over time: of nine persons reporting symptoms attributed to RF-EMF at T_0, only one still reported the same at T_1 and T_4, and two newly reported health complaints at T_4. In addition, about 12 % of the participants reported the notion of being EHS (without the condition of health complaints attributed to RF-EMF exposure) at T_4, and we observed that high RF-EMF risk and exposure perception, as well as self-reported symptoms and sleep disturbances at T_0 and T_1, were statistically significant risk factors for this condition.

To the best of our knowledge, this is the first epidemiological study investigating the time course of IEI-RF in a well-established general population cohort of adult individuals assessed at multiple time points over a long time period of follow-up, which enabled us to investigate the dynamic process of IEI-RF with 2 and 10 years of latency. Furthermore, by collecting data on perceived RF-EMF exposure and risk, and non-specific symptoms (i.e. symptom reporting and sleep disturbances) over the 10-year follow-up, we were well positioned to investigate the dynamics of several individual factors possibly related to IEI-RF.

Weakness of our study includes that it was not feasible to measure true exposure in our study participants and we were therefore not able to follow the time course of actual RF-EMF exposure. Because we asked for the “most important health complaint” attributed to RF-EMF exposure, we were also not able to reliably follow which exact symptoms were included into the attribution over time. Furthermore, given the sparseness of consistent “yes” data of IEI-RF over time, we did not estimate mutually adjusted multi-state Markov models. Finally, we could not assess the time course of EHS in the study popula-

tion due to the lack of EHS data at T_0 and T_1.

A previous longitudinal study conducted in Switzerland in 2008 and 2009 showed that only a minority of the participants who attributed health complaints to RF-EMF exposure (27 %) made the same declaration after one year (Röösli et al., 2010), and a longitudinal study conducted in Germany between 2004 and 2006 found a slightly larger proportion of participants (31 %) who did the same after two years of follow-up (Kowall et al., 2012). These results are consistent with what we found in our study, with a strong change in the population reporting symptoms attributed to RF-EMF exposure. Over the course of 10 years this translated to a 95 % probability of not attributing health complaints to RF-EMF exposure any more in persons who did so at baseline, and to a 1 % probability of acquiring such an attribution in those who did not attribute at baseline.

The estimated prevalence of EHS as well as of IEI-RF and IEI-EMF in the general population is uncertain (Eltiti et al., 2007; Hillert et al., 2002; Karvala et al., 2018; Levallois et al., 2002; Schreier et al., 2006). In our cohort we observed a lower prevalence of IEI-RF compared to previous studies. Kowall et al. estimated the prevalence of IEI-RF to be 8.7 % (2004) and 7.2 % (2006) based on attribution of health complaints to RF-EMF exposure (Kowall et al., 2012). However, this study was limited to only focusing on RF-EMF exposure from mobile phone base stations. Röösli et al. reported an IEI-RF prevalence of 13.0 % and 14.3 % in 2008 and 2009, respectively, when evaluating health complaints generally attributed to electromagnetic pollution in everyday life. In that same study, EHS prevalence was also assessed based on a question targeting the notion of being EHS. Based on that question, the EHS prevalence was lower (8.6 % and 7.7 % in 2008 and 2009, respectively), and lower than what we found in our general population cohort in 2021 (12.1 %) using a similar question to define EHS (Röösli et al., 2010). We provided data about prevalence of IEI-RF and EHS by year, in our and in the named other studies, in Supplementary Table 4.

The following factors could contribute to the disagreement between the estimated prevalence of IEI-RF and EHS: first, the term “electromagnetic hypersensitivity” may not be familiar to all individuals in our Dutch cohort. Interestingly, of the 11 participants reporting IEI-RF in 2021, only 6 defined themselves as EHS when answering the question targeting the notion of being electromagnetic hypersensitive in the same year. In contrast, only 6 out of 108 participants defining themselves as EHS also attributed own health complaints to RF-EMF exposure in the same year. These results indicated that our participants provided a different interpretation of IEI-RF and the notion of being EHS, thus suggesting that future studies should carefully design their survey and questionnaire in order to obtain the most comprehensive and accurate estimates of IEI-RF and EHS prevalence in the study population. Due to the considerable heterogeneity in the criteria used by researchers to define EHS, reports of EHS as well as of IEI-RF prevalence in different populations may be difficult to align (Baliatsas et al., 2012).

Second, people who self-describe as electromagnetic hypersensitive may avoid exposure and thus not be attributing symptoms. As a consequence, one could expect a higher prevalence for being sensitive than for experiencing symptoms that can be attributed. At the same time, the exact wording of the question in the questionnaire can play a role. It might be easier for participants who generally consider themselves sensitive to any (environmental) stressors to perceive themselves also electromagnetic hypersensitive. On the other hand, by asking for health complaints attributed to specific RF-EMF sources, it might be less likely for those who generally consider themselves sensitive to say "yes".
Third, we did not consider in our analyses health complaints attributed to extremely low frequency electric and magnetic fields (ELF-EMF), such as from powerlines or electric appliances. Therefore, we cannot exclude that these additional EMF sources may have influenced the proportion of participants defining themselves as sensitive to RF-EMF exposure at T_4. However, information on health complaints attributed to ELF-EMF was available at T_0 and T_1 and showed that only 2 out of 892 participants reported at least one symptom that they attributed to ELF-EMF exposure. This result suggested that an underestimation of EHS prevalence due to missing information on ELF-EMF at T_4 was unlikely to have been large in our study.
Finally, given the sample size of the AMIGO sub-cohort, the difference in estimated prevalence of EHS and IEI-RF should be interpreted cautiously.

Three main pathways have been hypothesized to explain what underlies EHS or IEI-RF: first, the biological pathway outlines that participants' RF-EMF exposure causes symptoms (Dieudonné, 2020). Presumably, for symptoms to go away, exposure would need to be attenuated. Given that we did not measure true RF-EMF exposure of our participants over time, we are limited in our ability to explore this exposure attenuation hypothesis in detail. However, it has been shown that one's own exposure is primarily driven by the own use of devices, in particular when calling with mobile phones (van Wel et al., 2021). Exposure reduction over time thus should entail that participants are aware of their own behavior changes and thus one would expect that their perceived exposure would be reduced as well. However, persons who attributed symptoms to RF-EMF exposure at T_0 or T_1, but not at T_4, tended to report higher exposure perception at T_4 than at the two previous time points, which does not fit this hypothesized pattern. Of note, current evidence is limited regarding a biological pathway in causing symptoms (French Agency for Food, Environmental and Occupational Health & Safety (ANSES), 2013; SSM's Scientific Council on Electromagnetic Fields, 2021). Second, the cognitive pathway hypothesizes that perceived exposure and risk promote a nocebo response that generates symptoms (Dieudonné, 2020). Ample experimental evidence supports nocebo effects (Martens et al., 2017; Szemerszky et al., 2010), although duration of such induced health problems have rarely been assessed. In our study, participants with higher risk and expo-

sure perception were somewhat more likely to transition towards attributing symptoms, indicating that nocebo effects may be relevant. Contrasting this, the observation that study participants reporting IEI-RF at T_0 and T_1, but not at T_4, overall increased (and not decreased) exposure and risk perception over time, does not support the cognitive hypothesis. Alternatively, symptoms triggered by nocebo effects may not be persistent. A recent qualitative study on IEI-EMF subjects suggested symptom reports preceded EMF risk perception which also contradicts the cognitive pathway (Dieudonné, 2016). As a third hypothesized pathway, symptoms may be attributed to RF-EMF exposure to help explain a health problem and reduce uncertainty regarding the underlying cause (attributive hypothesis) (Dieudonné, 2020). Prevalence of non-specific symptom reporting based on the 4DSQ-S score was 91, 91, and 95 % of the participants reporting at least one non-specific symptom at T_0, T_1, and T_4, respectively. Given that we cannot explore whether symptom reporting or risk perception came first, we are not able to prove or disprove this pathway. Nevertheless, the high prevalence of symptom reports means that this pathway was possible in our population.

Conclusion

In our study we found that IEI-RF appears to be a more transient phenomenon than previously assumed. At each time point, about 1 % of study participants reported health complaints that they attributed to RF-EMF exposure and, overall, participants had a 95 % chance of transitioning from “yes” to “no” over a time course of 10 years, and a chance of 1 % of transitioning from “no” to “yes”. Participants with a high perception of both RF-EMF exposure and health risk had a general tendency to transition more frequently between states.

RF-EMF perceptions as well as non-specific symptom reporting and sleep disturbances at baseline were predictive for the notion of being EHS at 10 years follow-up, regardless of whether reporting health complaints attributed to RF-EMF exposure. The knowledge regarding predictors of these dynamics may provide opportunities for future risk communication and prevention, particularly targeting those individuals in the population who consistently attribute health complaints to RF-EMF exposure over time.

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Table 1. Characteristics of the participants at T_0 (2011/2012) in the sub-cohort of AMIGO (n=892).

	Cohort at T_0 (2011/2012)	
	n (%)	Mean (SD)
Sex		
male	424 (47.5)	
female	468 (52.5)	
Age (in years)		50.4 (9.0)
Highest level of education attained[a]		
low	157 (17.6)	
intermediate	266 (29.8)	
high	469 (52.6)	
Urbanicity level[b]		
very highly urban	117 (13.1)	
highly urban	282 (31.6)	
moderately urban	238 (26.7)	
little urban	177 (19.8)	
non-urban	78 (8.8)	
Mobile phone use		
nonuser	234 (26.2)	
user	658 (73.8)	

[a]Low: primary school, lower vocational training or lower secondary education; intermediate: intermediate vocational education or intermediate/higher secondary education; high: higher vocational education or university degree.
[b]Very highly urban: ≥ 2,500 addresses per km^2; highly urban: 1,500–2,500 addresses per km^2; moderately urban: 1,000–1,500 addresses per km^2; little urban: 500–1,000 addresses per km^2; non-urban: < 500 addresses per km^2.

Table footnote for publication: Characteristics of the participants at baseline (T_0: 2011/2012) in the sub-cohort of AMIGO (n=892).

Table 2. Perceived RF-EMF exposure, perceived RF-EMF risk, and symptom characteristics at T_0 (2011/2012), T_1 (2013), and T_4 (2021) in the sub-cohort of AMIGO (n=892).

	Cohort at T_0 (2011/2012)		Cohort at T_1 (2013)		Cohort at T_4 (2021)	
	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)
Perceived RF-EMF exposure[a] low perception high perception	 847 (94.9) 45 (5.1)		 826 (92.6) 66 (7.4)		 718 (80.5) 174 (19.5)	
Perceived RF-EMF risk[b] low perception high perception	 828 (92.8) 64 (7.2)		 805 (90.2) 87 (9.8)		 767 (86.0) 125 (14.0)	
4DSQ-S score		5.9 (5.3)		5.7 (4.9)		7.0 (5.1)
MOS sleep index		26.7 (14.3)		27.0 (14.1)		26.4 (14.8)

[a]The cut-off point for low/high perception was based on the distribution of perceived RF-EMF exposure at T_0 (low: 0^{th}-90^{th} percentile, high: 90^{th}-100^{th} percentile, cut-off point=12).
[b]The cut-off point for low/high perception was based on the distribution of perceived RF-EMF risk at T_0 (low: 0^{th}-90^{th} percentile, high: 90^{th}-100^{th} percentile, cut-off point=12).

Abbreviations: 4DSQ-S, somatization scale of the Four-Dimensional Symptom Questionnaire; MOS, Medical Outcomes Study; n, number of participants; SD, standard deviation.

Table footnote for publication: Distribution of perceived RF-EMF exposure and perceived RF-EMF risk at T_0 (2011/2012), T_1 (2013), and T_4 (2021) and mean (standard deviation) of non-specific symptoms (4DSQ-S score) and sleep disturbances (MOS sleep index) at T_0 (2011/2012), T_1 (2013), and T_4 (2021) in the sub-cohort of AMIGO (n=892).

Table 3. Prevalence of self-reported health complaints attributed to RF-EMF exposure (IEI-RF) at T_0 (2011/2012), T_1 (2013), and T_4 (2021), and self-reported notion of being electromagnetic hypersensitive (EHS) at T_4 (2021), in the sub-cohort of AMIGO (n=892).

	Cohort at T_0 (2011/2012)		Cohort at T_1 (2013)		Cohort at T_4 (2021)	
	n	%	n	%	n	%
Health complaints attributed to RF-EMF exposure (IEI-RF)						
no	883	99.0	882	98.9	881	98.8
yes	9	1.0	10	1.1	11	1.2
Self-reported notion of being electromagnetic hypersensitive (EHS)	-		-		784	87.9
no	-		-		108	12.1
yes						

Table footnote for publication: Distribution of health complaints attributed to RF-EMF exposure (IEI-RF) at T_0 (2011/2012), T_1 (2013), and T_4 (2021) and self-reported notion of being electromagnetic hypersensitive (EHS) at T_4 (2021) in the sub-cohort of AMIGO (n=892).

Table 4. Associations of self-reported health complaints attributed to RF-EMF exposure (IEI-RF) with perceived RF-EMF exposure (Model 1), perceived RF-EMF risk (Model 2), 4DSQ-S score (Model 3), MOS sleep index (Model 4), evaluated with multi-state models with transitions at T0, T1, and T4 in the sub-cohort of AMIGO (n=892).

	transition	HR 95% CI
Model 1[a]		
Perceived RF-EMF exposure		
low perception	no-yes	1
	yes-no	1
high perception	no-yes	4.11 (0.87;19.53)
	yes-no	0.56 (0.11;2.82)
Model 2[a]		
Perceived RF-EMF risk		
low perception	no-yes	1
	yes-no	1
high perception	no-yes	3.81 (0.76;19.18)
	yes-no	0.46 (0.10;2.16)
Model 3[a]		
4DSQ-S Score		
	no-yes	1.07 (0.95;1.20)
	yes-no	0.96 (0.85;1.08)
Model 4[a]		
MOS Sleep Index		
	no-yes	0.98 (0.91;1.05)
	yes-no	0.93 (0.87;1.01)

[a]Adjusted for sex and age at T_0.

Abbreviations: 4DSQ-S, somatization scale of the Four-Dimensional Symptom Questionnaire; MOS, Medical Outcomes Study; HR, Hazard Ratios; CI, Confidence Interval.

Table footnote for publication: Results from four multi-state Markov models representing how individuals in the sub-cohort transitioned between two states defined by the presence ("yes") or absence ("no") of IEI-RF. We included perceived RF-EMF exposure (Model 1), perceived RF-EMF risk (Model 2), 4DSQ-S score (Model 3), and MOS sleep index (Model 4) as time-dependent risk factors to investigate potential time-variant effects on transition rates, adjusted for sex and age.

Table 5. Associations of self-reported notion of being electromagnetic hypersensitive (EHS) at T_4 with perceived RF-EMF exposure (Model 5), perceived RF-EMF risk (Model 6), 4DSQ-S score (Model 7), MOS sleep index (Model 8), and perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, MOS sleep index mutually adjusted (Model 9 with minimal adjustment; Model 10 with full adjustment) assessed at T_0.

	Model 5[a]	Model 6[a]	Model 7[a]	Model 8[a]	Model 9[a]	Model 10[b]
	OR 95 % CI	OR 95 % CI	OR 95 % CI	OR 95 % CI	OR 95 % CI	OR 95 % CI
Perceived RF-EMF exposure low perception high perception	1 4.17 (2.10;8.00)	-	-	-	1 2.39 (1.09;4.97)	1 2.38 (1.08;5.01)
Perceived RF-EMF risk low perception high perception	-	1 4.08 (2.26;7.17)	-	-	1 2.92 (1.50;5.49)	1 3.07 (1.57;5.83)
4DSQ-S Score	-	-	1.07 (1.03;1.10)	-	1.05 (1.01;1.09)	1.05 (1.00;1.09)
MOS Sleep Index	-	-	-	1.02 (1.00;1.03)	1.01 (0.99;1.02)	1.01 (0.99;1.02)

[a]Adjusted for sex and age at T_0.
[b]Adjusted for sex, age, the highest level of education attained, urbanicity level, and self-reported mobile phone use at T_0.

Table footnote for publication: Results from logistic regression on the association between EHS at T_4 and perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, MOS sleep index, assessed at T_0. We estimated four logistic regression models including each independent variable separately, and two mutually adjusted logistic regression models (with minimal and full adjustment) where perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, MOS sleep index were considered simultaneously.

Table 6. Associations of self-reported notion of being electromagnetic hypersensitive (EHS) at T4 with perceived RF-EMF exposure (Model 11), perceived RF-EMF risk (Model 12), 4DSQ-S score (Model 13), MOS sleep index (Model 14), and perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, MOS sleep index mutually adjusted (Model 15 with minimal adjustment; Model 16 with full adjustment) assessed at T1.

	Model 11[a]	Model 12[a]	Model 13[a]	Model 14[a]	Model 15[a]	Model 16[b]
	OR 95 % CI	OR 95 % CI	OR 95 % CI	OR 95 % CI	OR 95 % CI	OR 95 % CI
Perceived RF-EMF exposure low perception high perception	1 2.85 (1.53;5.10)	-	-	-	1 1.64 (0.79;3.28)	1 1.84 (0.87;3.72)
Perceived RF-EMF risk low perception high perception	-	1 3.02 (1.74;5.09)	-	-	1 2.36 (1.24;4.36)	1 2.41 (1.25;4.51)
4DSQ-S Score	-	-	1.06 (1.02;1.10)	-	1.04 (0.99;1.09)	1.03 (0.99;1.08)
MOS Sleep Index	-	-	-	1.02 (1.00;1.03)	1.01 (0.99;1.03)	1.01 (0.99;1.03)

[a]Adjusted for sex and age at T_0.
[b]Adjusted for sex, age, the highest level of education attained, urbanicity level, and self-reported mobile phone use at T_0.

Table footnote for publication: Results from logistic regression on the association between EHS at T_4 and perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, MOS sleep index, assessed at T_1. We estimated four logistic regression models including each independent variable separately, and two mutually adjusted logistic regression models (with minimal and full adjustment) where perceived RF-EMF exposure, perceived RF-EMF risk, 4DSQ-S score, MOS sleep index were considered simultaneously.

Figure 1. Flow of participants. We included in the analyses participants who filled in questionnaires at time points T_0, T_1, and T_4.

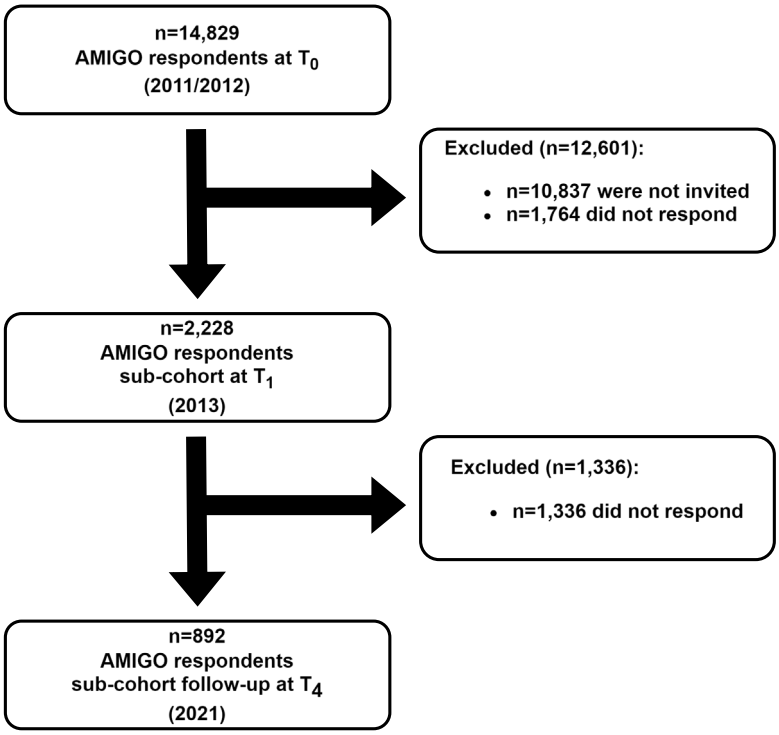

Figure footnote for publication: Flow of participants. In the sub-cohort of AMIGO, we included participants who filled in questionnaires at time points T0, T1, and T4 (n=892 of 2,228 invited participants).

SUPPLEMENTARY MATERIAL

Title: Time course of health complaints attributed to RF-EMF exposure and predictors of electromagnetic hypersensitivity over 10 years in a prospective cohort of Dutch adults

Authors: Eugenio Traini[1], Astrid L. Martens[2], Pauline Slottje[3,4], Roel C.H. Vermeulen[1], Anke Huss[1]

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Supplementary Table 1. Characteristics of the participants at T_0 (2011/2012) in the full cohort of AMIGO (n=14,829).

	Cohort at T_0 (2011/2012)	
	n (%)	Mean (SD)
Sex		
male	6,561 (44.2)	
female	8,268 (55.8)	
Age (in years)		50.6 (9.3)
Highest level of education attained[a]		
low	4,546 (30.6)	
intermediate	4,627 (31.2)	
high	5,656 (38.2)	
Urbanicity level		
very highly urban	1,263 (8.5)	
highly urban	3,307 (22.3)	
moderately urban	3,228 (21.8)	
little urban	3,615 (24.4)	
non-urban	3,416 (23.0)	
Mobile phone use		
nonuser	4,384 (29.6)	
user	10,278 (69.3)	
no answer	167 (1.1)	

[a]Low: primary school, lower vocational training or lower secondary education; intermediate: intermediate vocational education or intermediate/higher secondary education; high: higher vocational education or university degree.
[b]Very highly urban: ≥ 2,500 addresses per km^2; highly urban: 1,500–2,500 addresses per km^2; moderately urban: 1,000–1,500 addresses per km^2; little urban: 500–1,000 addresses per km^2; non-urban: < 500 addresses per km^2.Table footnote for publication: Characteristics of the participants at baseline (T_0: 2011/2012) in the full cohort of AMIGO (n=14,829).

Supplementary Table 2. Transitions of health complaints attributed to RF-EMF exposure (IEI-RF) that are observed between T_0 and T_1 (A), T_1 and T_4 (B), and any consecutive time points T_0, T_1, T_4 (C).

A.

from \ to	no	yes
no	875	8
yes	7	2

B.

from \ to	no	yes
no	874	8
yes	7	3

C.

from \ to	no	yes
no	1749	16
yes	14	5

Table footnote for publication: The observed transitions, that is the number of times each pair of states of health complaints attributed to RF-EMF exposure (IEI-RF) were observed in successive observation times between T_0 and T_1, T_1 and T_4, and any consecutive time points T_0, T_1, T_4.

Supplementary Table 3. Fitted transition probabilities of health complaints attributed to RF-EMF exposure (IEI-RF) over different time intervals (t=2, 10 years).

	from \ to	no	yes
t=2	no	0.994 (0.989;0.997)	0.006 (0.004;0.010)
	yes	0.464 (0.283;0.687)	0.536 (0.313;0.717)
t=10	no	0.987 (0.978;0.991)	0.013 (0.008;0.021)
	yes	0.945 (0.808;0.986)	0.055 (0.014;0.192)

Table footnote for publication: Fitted transition probabilities for each pair of states of health complaints attributed to RF-EMF exposure (IEI-RF) over different time intervals (t=2, 10 years).

Supplementary Table 4. Prevalence of IEI-RF and EHS by year, respectively, in this and other studies.

	Prevalence (%) of IEI-RF	Prevalence (%) of EHS	Year
Kowall et al. 2012[a]	8.7		2004
	7.2		2006
Roosli et al. 2010[b]	13.0	8.6	2008
	14.3	7.7	2009
Traini et al. 2022[c]	1.0		2011/2012 (T_0)
	1.1		2013 (T_1)
	1.2	12.1	2021 (T_4)

[a]Prevalence of IEI-RF was estimated based on the question: "Do you feel compromised in your health because of (mobile phone base station) electromagnetic fields?". Possible answers were "yes" or "no".
[b]Prevalence of IEI-RF was estimated based on the question: "Do you think that you develop detrimental health symptoms due to electromagnetic pollution in everyday life?"; those answering "yes" but not declaring to be hypersensitive were called "attributers". Prevalence of EHS was estimated based on the question: "Are you electrohypersensitive?"; those answering "yes" were considered electromagnetic hypersensitive.
[c]Prevalence of IEI-RF was estimated based on the question: "Do you currently have health complaints that you attribute to the environment" and "if so, to what environmental factors/sources, select from the following or describe another factor/source" ((1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones; (3) electromagnetic fields from cordless phones) at T0 and T1, and based on the question: "Do you currently have health complaints that you attribute to the environment" and "if so, to what environmental factors/sources, select from the following or describe another factor/source" ((1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones, cordless phones and other wireless devices, (e.g. laptop, tablet); (3) electromagnetic fields from 5G technology) at T4; prevalence of EHS was estimated at T4 estimated based on the question: "Are you electrohypersensitive?".

Table footnote for publication: Data about prevalence of IEI-RF and EHS by year, in this and other studies, including questions asked to assess IEI-RF and EHS in each study.

Supplementary Figure 1. A multi-state Markov process illustrated along the time axis with two separate states ("no", "yes") of IEI-RF, indicated by the nodes. The defined model allows transitions between states at each time point, with $q_{no\text{-}yes}$ and $q_{yes\text{-}no}$ representing transition intensities for the two state switches.

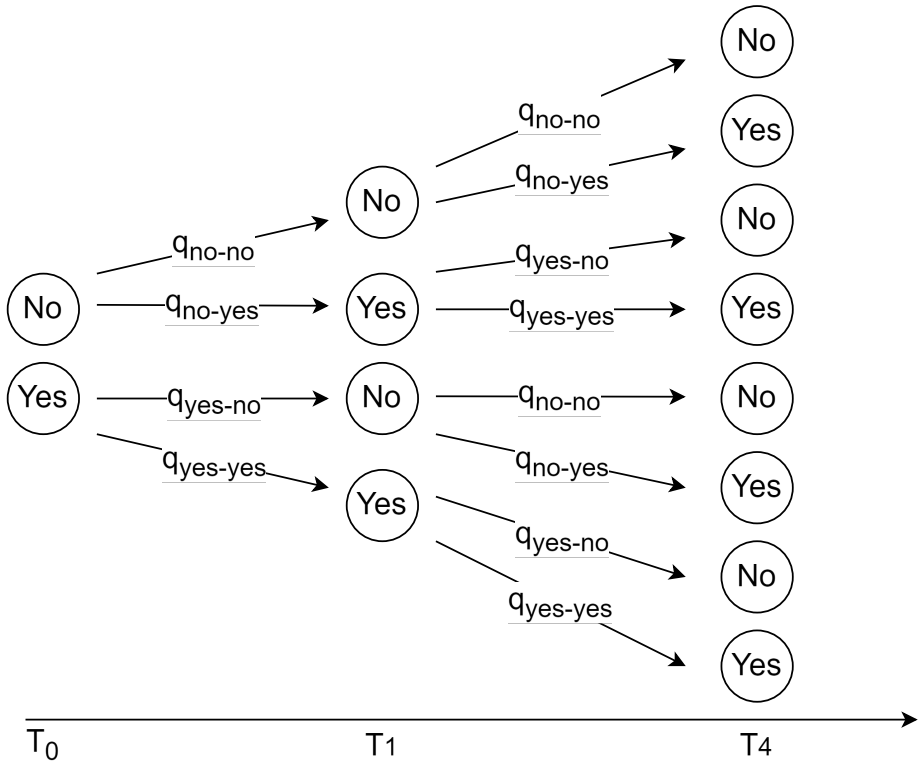


Figure footnote for publication: A multi-state Markov process illustrated along the time axis with two separate states ("no", "yes") of IEI-RF, indicated by the nodes.

Supplementary Figure 2. Distribution of perceived RF-EMF exposure and risk at T_0, T_1, and T_4.

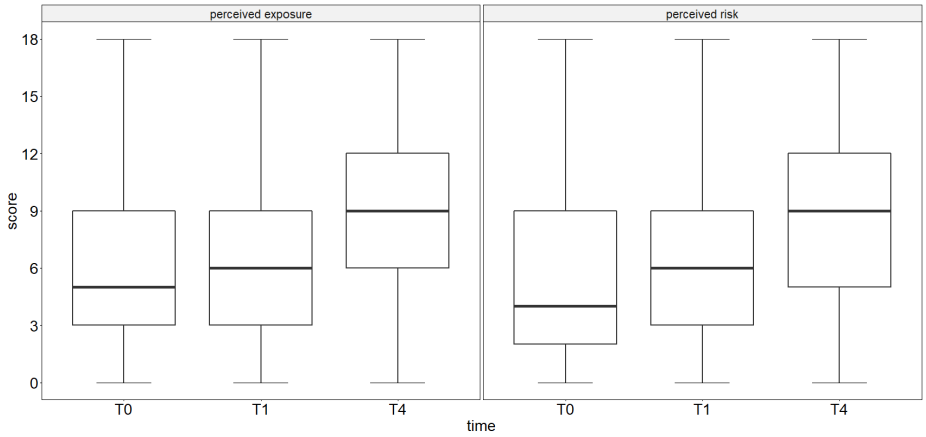
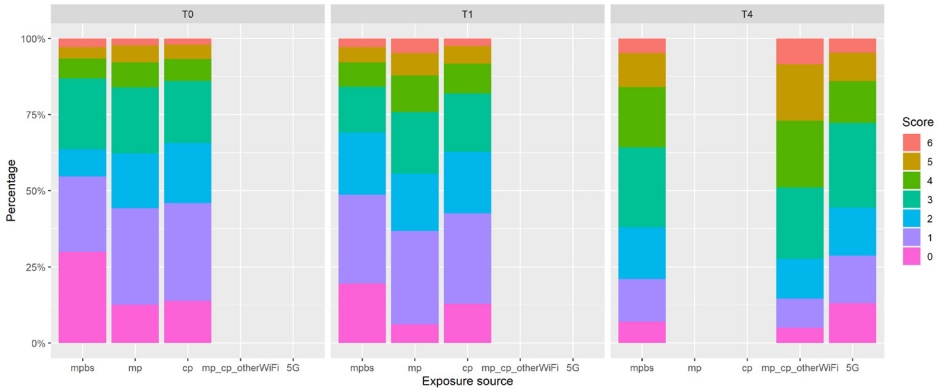


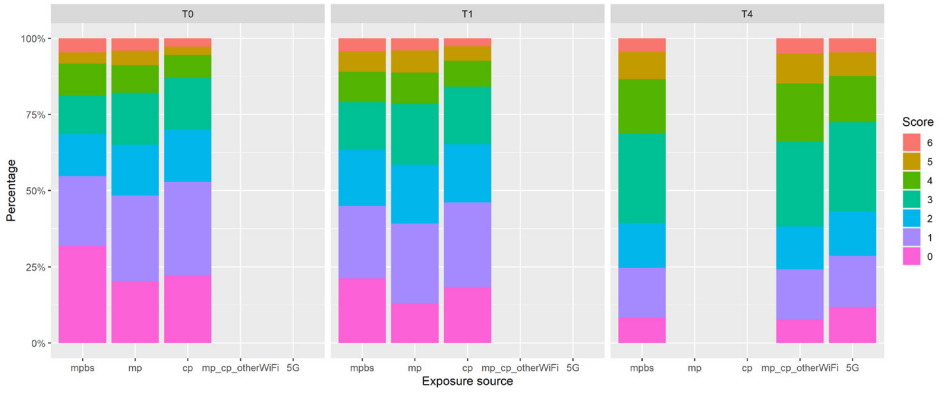
Figure footnote for publication: Distribution of perceived RF-EMF exposure and perceived RF-EMF risk at T_0, T_1, and T_4. The boxplots show median, 1st quartile, and 3rd quartile, with whiskers extending to the most extreme data point which is no more than 1.5 times the interquartile range (IQR)

Supplementary Figure 3. Distribution of scores (scale of 0-6 where 0=not at all, 6=very much) of perceived RF-EMF exposure (A) and risk (B) grouped by exposure source at T0, T1, and T4.

A.



B.



Abbreviations: mpbs, mobile phone base stations; mp, mobile phones ; cp, cordless phones ; mp_cp_otherWiFi, mobile phones, cordless phones, and other wireless devices; 5G, 5 Generation technology.

Figure footnote for publication: Distribution of scores of perceived RF-EMF exposure (A) and perceived RF-EMF risk (B), grouped by exposure source at T0, T1, and T4. Perceived exposure with respect to RF-EMFs (amongst other environmental exposures) was assessed at T0 and T1 with the question: "To what extent do you think you are exposed to: (1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones; (3) electromagnetic fields from cordless phones; (on a scale of 0-6, where 0=not at all and 6=very much)?", and at time point T4 with the question: "To what extent do you think you are exposed to: (1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones, cordless phones and other wireless devices, (e.g. laptop, tablet); (3) electromagnetic fields from 5G technology; (on a scale of 0-6, where 0=not at all and 6=very much)?".
Perceived risk with respect to RF-EMFs (amongst other specified environmental factors) was assessed at T0 and T1 with the question: "To what extent do you think that ((1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones; (3) electromagnetic fields from cordless phones) pose a risk to the health in everyday circumstances? (on a scale of 0-6, where 0=not at all and 6=very much)", and at time point T4 with the question: "To what extent do you think that ((1) electromagnetic fields from mobile phone base stations, radio or TV; (2) electromagnetic fields from mobile phones, cordless phones and other wireless devices, (e.g. laptop, tablet); (3) electromagnetic fields from 5G technology) pose a risk to the health in everyday circumstances? (on a scale of 0-6, where 0=not at all and 6=very much)".

Supplementary Figure 4. The dynamic process of IEI-RF with 2 and 10 years of latency, with the nodes representing the two states ("no", "yes") of IEI-RF. The number of participants in each state at T_0, T_1, and T_4 is indicated in the each node.

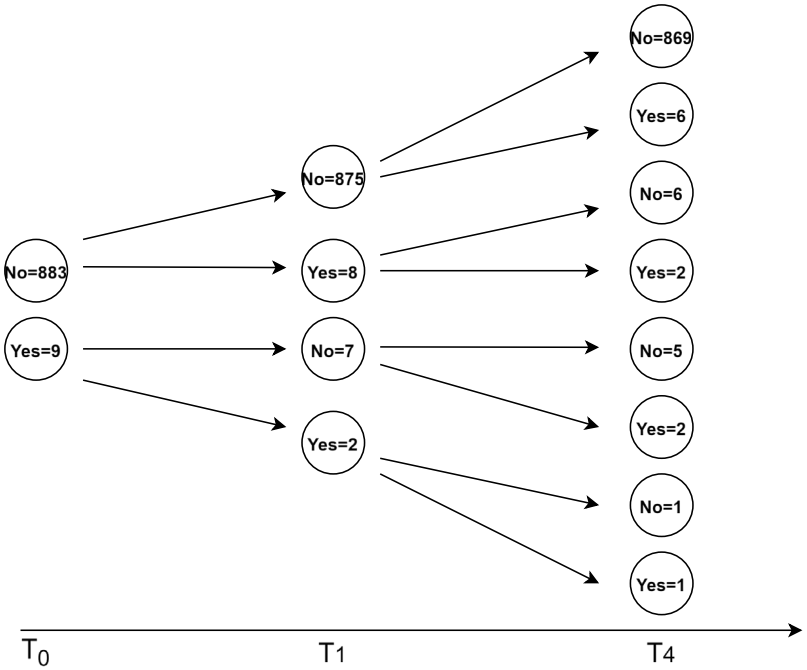
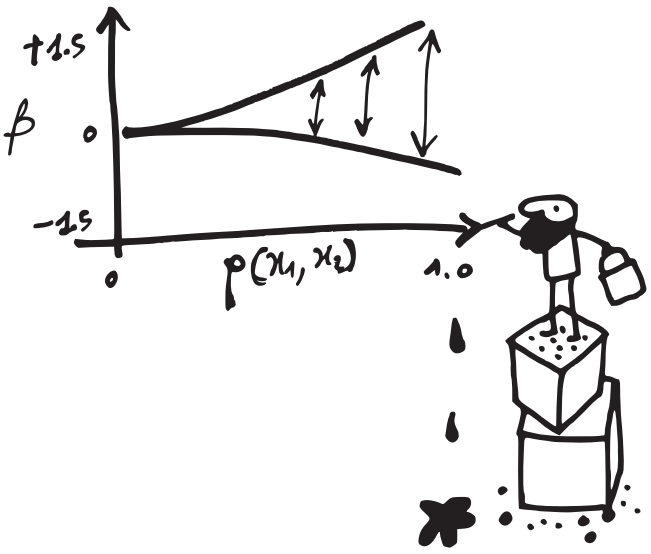


Figure footnote for publication: The multi-state Markov process illustrated along the time axis with two separate states ("no", "yes") of IEI-RF, showing the number of participants at T_0, T_1, and T_4 in each node.


+1.5
β
0
-1.5
0
p(x1, x2)
1.0

Chapter 4: A multi-pollutant approach to estimating causal effects of air pollution mixtures on overall mortality in a large, prospective cohort

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Abstract

Background: Several studies have confirmed associations between air pollution and overall mortality, but it is unclear to what extent these associations reflect causal relationships. Moreover, few studies to our knowledge have accounted for complex mixtures of air pollution. In this paper, we evaluate causal effects of a mixture of air pollutants on overall mortality in a large, prospective cohort of Dutch individuals.

Methods: We evaluated 86,882 individuals from the LIFEWORK study, assessing overall mortality between 2013-2017 through national registry linkage. We predicted outdoor concentration of five air pollutants ($PM_{2.5}$, PM_{10}, NO_2, $PM_{2.5}$ absorbance, oxidative potential) with land-use regression. We used logistic regression and mixture modeling (weighted quantile sum and boosted regression tree models) to identify potential confounders, assess pollutants relevance in the mixture–outcome association, and investigate interactions and non-linearities. Based on these results, we built a multivariate generalized propensity score model to estimate causal effects of pollutant mixtures.

Results: Regression model results were influenced by multicollinearity. Weighted quantile sum and boosted regression tree models indicated that all components contributed to a positive linear association with the outcome, with $PM_{2.5}$ being the most relevant contributor. In the multivariate propensity score model, $PM_{2.5}$ (OR=1.18, 95% CI:1.08,1.29) and PM_{10} (OR=1.02, 95% CI:0.91,1.14) were associated with increased odds of mortality per interquartile range increase.

Conclusion: Using novel methods for causal inference and mixture modeling in a large prospective cohort, this study strengthened the causal interpretation of air pollution effects on overall mortality, emphasizing the primary role of $PM_{2.5}$ within the pollutant mixture.

Introduction

Exposure to air pollution has been found to be associated with higher mortality rates in several studies over the last decades (Brook et al., 2010; Di et al., 2017; *World Health Organization. Ambient (Outdoor) Air Quality and Health. Fact Sheet No. 313. Geneva: World Health Organization.*, 2015), and associations have been reported even at low levels of exposure (Beelen et al., 2013; Chen et al., 2021; Di et al., 2017; Strak et al., 2021; Wei et al., 2021). However, to improve our understanding of these associations and to facilitate the development of better targeted public health regulations and interventions, it is important to determine to which extent these associations reflect causal relationships (*HEI Health Effect Institute. Strategic Plan for Understanding the Health Effects of Air Pollution. 2020–2025. Fist Draft May 2019. Available Online: Https://Www.Healtheffects. Org/Sites/Default/Files/First-Draft-HEI-StrategicPlan2020-2025.Pdf*, 2019).

When evaluating the health effects of environmental exposures such as air pollutants, it is important to account for the co-occurrence of multiple environmental constituents, present in the real world as a complex mixture (Dominici et al., 2010a). To evaluate the causal effects of air pollution on health, it is thus critical that studies account for this complex nature of exposure. This approach would allow identifying relevant contributors within the mixture as well as detecting potential interactions between pollutants. Several analytical methods have been proposed to deal with statistical challenges inherent to mixtures, such as co-exposure confounding, high correlation, and interaction between components of the mixture (Billionnet et al., 2012; Stafoggia et al., 2017; Taylor et al., 2016). Furthermore, regulatory policies are still mostly designed to regulate one pollutant or one source at the time, whereas more complex evaluations regarding causality may possibly lead to a more targeted regulatory policy (*HEI Health Effect Institute. Strategic Plan for Understanding the Health Effects of Air Pollution. 2020–2025. Fist Draft May 2019. Available Online: Https://Www.Healtheffects.Org/Sites/Default/Files/First-Draft-HEI-StrategicPlan2020-2025.Pdf*, 2019). As such, there is a need to improve our understanding of the causal effects of environmental mixtures evaluated as a complex exposure situation of high-dimensional data (Carone et al., 2020; Dominici & Zigler, 2017).

In this study, we investigated the effects of a mixture of five pollutants on overall mortality in a large population-based cohort of Dutch individuals where air pollution exposure has been assessed through state-of-the-art methodologies. We adopted a pluralistic approach exploring the pollutant mixture with targeted methods for high-dimensional exposures, including boosted regression tree and weighted quantile sum models, and investigated the causal relationships between multiple pollutants and mortality with novel extensions of propensity score approaches.

Material and methods

Study participants and outcome definition

We used data from the LIFEWORK study, a large prospective cohort consortium comprising nearly 90,000 participants aged 18+ living in the Netherlands. LIFEWORK was designed as a federated study resulting from the integration of three existing Dutch cohorts: the Nightingale study, initiated in 2011 and the largest contributor to the LIFEWORK study (68%), the Occupational and Environmental Health Cohort Study (AMIGO) (17%) started in 2011, and the European Prospective Investigation into Cancer and Nutrition in the Netherlands (EPIC-NL) (15%), established between 1993 and 1997. Data were collected from each cohort between 2011 and 2012 (baseline questionnaires for AMIGO and Nightingale, follow-up questionnaire for EPIC-NL) and pooled to set up the LIFEWORK cohort, setting the baseline at January 1st, 2013. The rationale, study design and participant recruitment in LIFEWORK were discussed in detail elsewhere (Beulens et al., 2010; Pijpe et al., 2014; Reedijk et al., 2018; Slottje et al., 2014). The contributing subcohorts were approved by the local research ethics review committee or institutional review board (AMIGO and EPIC-NL Prospect by the committee at the University Medical Center Utrecht; EPIC-NL MORGEN by the committee at TNO Nutrition and Food Research; and Nightingale by the committee at the Netherlands Cancer Institute), and participants signed an informed consent form for each subcohort prior to enrolment.
From the original 88,466 LIFEWORK participants, we excluded 683 individuals with missing exposure information (their residential address either was incomplete; fell in the sea, river or another water course; or at least one predictor for the land-use regression models was missing), 378 with reported emigration during the study, and 523 with no informed consent to link to the Municipal Personal Records Database (GBA). The GBA is a centralized automated population registration system that holds information on residence (home address) and date of death of people who reside in the Netherlands as well as personal data on migration. After exclusions, the total population evaluated in this study consisted of 86,882 individuals.
The outcome of interest was all-cause mortality, assessed by ascertaining vital status from the Dutch Central Bureau of Statistics (CBS) and date of death over a 5-year follow-up period (1 January 2013 - 31 December 2017) via data linkage to the GBA.

Exposure assessment

We evaluated air pollution as a mixture of five components: particulate matter with aerodynamic diameter less than 2.5 µm ($PM_{2.5}$), particulate matter with aerodynamic diameter less than 10 µm (PM_{10}), a marker of diesel exhaust particulate ($PM_{2.5}$ absorbance), nitrogen dioxide (NO_2), and the oxidative potential estimated in $PM_{2.5}$ by dithiothreitol.
Land-use regression models were fitted to estimate outdoor concentrations of air pollutants at the home address for each participant, combining monitoring of air pollution at different locations and predictor variables obtained from spatial data (Hoek et al., 2008).

Model development has been described in detail elsewhere (Chen et al., 2021). Briefly, we developed land-use regression models based upon annual average concentrations of $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10} and NO_2 measured between October 2008 and April 2011 during three 14-day periods to account for seasonal variation. We conducted measurements in 20 European study areas at 20–40 sites for PM and at 40–80 sites per area for NO_2. The annual average ambient pollutant concentrations were estimated at addresses of study participants at baseline using as predictor variables data on traffic intensity, household density, land use and other study-area variables such as altitude and distance to the sea. The median model explained variance (R^2) ranged from 71% ($PM_{2.5}$) to 89% ($PM_{2.5}$ absorbance) (Beelen et al., 2013; Eeftens et al., 2012). Oxidative potential concentration was estimated based on a sampling period of three 2-week PM measurements carried out at 40 sites spread over the Netherlands and Belgium between February 2009 and February 2010 taking into account temporal variability. Land-use regression models for oxidative potential were estimated at participants' addresses at baseline and achieved an R^2 value of 60% (Yang et al., 2015).

Covariates

We selected potential confounders of the associations between air pollution and overall mortality *a priori* based on results from preliminary studies (Beelen et al., 2013; Chen et al., 2021; Eeftens et al., 2012). These potential confounders included age, sex, body mass index (BMI, weight (kg)/height $(m)^2$)), cardiovascular disease (CVD) diagnosis, chronic obstructive pulmonary disease (COPD) diagnosis, cancer diagnosis, smoking status (never, former, current), highest level of education attained (low, intermediate, high), the estimated monthly household income of the neighborhood based on income data provided by CBS in 2012 (www.cbs.nl), and the normalized difference vegetation index which quantifies vegetation density around each participant's address based on Landsat 8 satellite images taken in 2008 (Rhew et al., 2011).

Statistical analysis

Descriptive statistics of the study population were evaluated overall, and by levels of air pollution exposure. As the interest of this analysis was in pollutant mixtures, we identified profiles of pollutant mixture exposure through K-means cluster analysis. We evaluated correlation between pollution components by calculating Spearman's rank correlation coefficients.

We first evaluated the association between air pollution constituents and overall mortality with classical regression models, both independently (one model for each mixture component) as well as mutually adjusting pollutants in the same statistical model. In the primary analysis, mutual adjustment was performed by considering the full set of components available in the LIFEWORK cohort. Overall mortality was evaluated as a binary outcome (dead/alive) with logistic regression, estimating ORs for mortality risk, as well

as with Poisson and Cox models to account for the duration of follow-up and for possible changes in event rates over time. A sensitivity analysis was conducted using multiple imputation by chained equation (MICE) to impute missing values in the exposures (Buuren & Groothuis-Oudshoorn, 2011). Age, sex, BMI, smoking, and CVD diagnosis were specified as predictors in the algorithm for each incomplete exposure variable. An additional sensitivity analysis was performed by excluding individuals with baseline CVD diagnosis (angina, heart attack, transient ischemic attack, stroke, other heart conditions, defined according to ICD-9 and ICD-10), COPD, and cancer diagnosis. Last, we conducted a secondary analysis on overall mortality and a subset of components (NO_2, $PM_{2.5}$, PM_{10}) representing a group of already regulated pollutants based on existing legislation (*World Health Organization. Ambient (Outdoor) Air Quality and Health. Fact Sheet No. 313. Geneva: World Health Organization.*, 2015).

We used multiple regression models to identify confounders of the association to be evaluated in causal models. Specifically, we first evaluated a fully adjusted multiple regression model by adjusting for all covariates presented in the previous section and then removed those confounders that did not change any exposure coefficient by more than 10%. To assess the impact of multicollinearity of multiple regression estimates, we calculated variance inflation factors (VIFs).

To address issues of multicollinearity and to identify pollution constituents from clusters of correlated exposures that should be included in the causal analysis, we used weighted quantile sum and boosted regression tree models. In brief, these methods are techniques used in mixture modeling to identify the relative contribution of several exposures in the overall effect between the mixture and the outcome of interest, while accounting for high correlation structures (Carrico et al., 2015; Lampa et al., 2014). While both correlation analysis and multivariable regression can inform on the levels of correlation, neither of them can detect which covariates within the mixture are driving the associations, and to what extent. Weighted quantile sum summarizes the mixtures with a single index estimated as a weighted linear combination of the exposures and allows identifying the relative contribution of each mixture constituent. This technique makes the assumptions of linear associations on the quantile scale and of unidirectionality (all exposures-outcome associations are either positive or negative), but directly provides an estimate of the relative percent contribution of each exposure within the mixture (Carrico et al., 2015). Boosted regression tree, on the other hand, is a machine learning technique based on trees modeling that does not provide any estimate of exposures contribution but allows ranking their relative importance while relaxing assumptions of unidirectionality and linearity, strengthening the interpretation of the results from the weighted quantile sum. In addition, boosted regression tree provides a qualitative assessment of interactions importance (through the use of the measure called H-statistics), which can be used as an exploratory tool to detect 2-way or higher order interactions that should be incorporat-

ed in subsequent analyses (Bellavia et al., 2021; Lampa et al., 2014).
To estimate the causal effects of pollutant mixture on overall mortality we used propensity score methods, building the propensity scores from the set of confounders identified in the regression modeling (Rosenbaum & Rubin, 1983). Propensity score methods achieve balance across a set of confounders thus reducing the confounding effect in the exposure-outcome relation. To evaluate pollutants as continuous exposures, we used the generalized propensity scores extension, which handles single continuous exposures given a set of confounders (Hirano & Imbens, 2005; Imai & Dyk, 2004), under the assumption that exposures follow a normal distribution. We first used generalized propensity scores to generate weights for each continuous exposure separately (Greifer, 2017). Next, to account for the mixture nature of air pollution, we used the multivariate generalized propensity score, a novel extension of the generalized propensity score for multiple simultaneous continuous exposures implemented in the R package *mvGPS* (Williams & Crespi, 2020). Multivariate generalized propensity score has the advantage over generalized propensity score of simultaneously estimating weights for multivariate continuous exposures that are constructed as the ratio of the marginal density of the exposures to the conditional density (Williams & Crespi, 2020). Specifically, the multivariate generalized propensity score generates stabilized inverse probability of treatment weights (IPTWs) assuming a multivariate normal distribution for the simultaneous exposures. These weights have been shown to balance confounders and provide unbiased exposure–response estimates (Robins et al., 2000). To optimize propensity score weights and avoid possible effects due to extreme weights, the procedure allows to trim both the upper and lower bounds of the weights' distribution (Lee et al., 2011). We conducted the main analysis using the recommended weights threshold at the 99th percentile (Williams & Crespi, 2020), and evaluated other thresholds (0.97, 0.95) in sensitivity analyses. All analyses were conducted with the R statistical software, version 4.0.4. Computing code related to all analyses presented is publicly available at https://github.com/andreabellavia/causalpm, also presenting different approaches to deal with categorical confounders, option that is not automatized in the current version of the *mvGPS* package (1.2.1) and requires additional coding. All exposures were evaluated as continuous variables and results indicate changes per interquartile range width (IQRw) increase in mean air pollution exposure.

Results

Baseline characteristics of the study population, overall and by levels of air pollution exposures, are presented in Table 1. K-means clustering identified three groups as the optimal characterization of the mixture, with the clusters summarizing levels of low, moderate, and high exposure to air pollution. Individuals with higher levels of exposures were on average older, lived in areas with lower normalized difference vegetation index, and were more likely to be smokers. The Figure presents the correlation structure

between air pollution constituents at baseline, while eTable 1 provides the distribution of each pollutant at baseline. All mixture components were highly positively correlated with each other.

During 5 years of follow up we observed 1,071 deaths (1.2%). Results from logistic regression models are reported in Table 2 and eTable 2. Out of all potential confounders evaluated in fully adjusted models, only age, sex, BMI, smoking, and baseline CVD diagnosis met the criteria for confounding to be selected for inclusion in the final model (referred to, in tables, as minimally adjusted model). When mutually adjusting the full set of air pollution constituents in the same statistical model, both $PM_{2.5}$ and PM_{10} were associated with higher odds of mortality (respectively, OR=1.17, 95% CI:0.99,1.37; OR=1.21, 95% CI:1.03,1.42), even though VIFs for these coefficients were relatively high (Table 2). $PM_{2.5}$ absorbance was associated with a reduction in the odds of mortality, but the extremely high VIF associated with this coefficient suggests that this result might be due to (multi) collinearity. Results from the multivariable logistic regression model using MICE to impute the missing exposures showed no discrepancies from findings on complete cases (eTable 3). When mutually adjusting the models for a subset of air pollution constituents represented by NO_2, $PM_{2.5,}$ and PM_{10}, both $PM_{2.5}$ (OR=1.03, 95% CI:0.94,1.14) and PM_{10} (OR=1.06, 95% CI:0.95,1.17) showed a positive, albeit much weaker, association with overall mortality (eTable 4). We observed negligible differences when excluding individuals with baseline CVD, and when using Poisson (data not shown) or Cox models (eTable 5). We therefore chose to only present results from logistic regression, as this allows a direct comparison with the statistical methods we used in our study to explore causal relationships, for which time-to-event models are not currently available.

To evaluate the mixture of pollutants while accounting for the strong correlations, we estimated the relative contribution of each exposure in the mixture–outcome association with boosted regression tree and weighted quantile sum models. In the boosted regression tree model, which provides a non-parametric estimation that accounts for non-linearities and interactions, all measures of H-statistics were consistently low, indicating a negligible impact of interactions in the mixture–outcome association (eFigure 1), and confirmed that exposure–response relationships were mostly linear and positive or null for all mixture components (data not shown). As such, weighted quantile sum assumptions were met, and this method could be used to provide an accurate estimate of the relative importance of the mixture components. Estimates of weighted quantile sum weights, presented in eFigure 2, show a prominent role of $PM_{2.5}$ in the association, greatly surpassing the contribution of PM_{10} and other components of the mixture. Moreover, the negligible weight associated with $PM_{2.5}$ absorbance indicates that the negative association observed in multiple regression for that variable is likely due to (multi) collinearity. The association between the overall mixture and mortality, estimated by the weighted quantile sum index, was negligible in our population (β=0.01, 95% CI:-

0.03,0.04) (eFigure 3).
Based on results from multiple regression and mixture modeling, we built propensity score models using the minimal set of confounders (age, sex, BMI, smoking, CVD diagnosis), and all exposures were included in the models as continuous covariates, thus evaluating their linear effect on the outcome. Furthermore, based on results from boosted regression tree and weighted quantile sum models, we excluded $PM_{2.5}$ absorbance from the analysis to limit the impact of multicollinearity on the results.

Table 3 presents results from the univariate and multivariate generalized propensity score models, with the recommended weights trimming at 0.99. All exposures met the normality distribution assumption required by these techniques. $PM_{2.5}$ was associated with increased odds of mortality (OR=1.18, 95% CI:1.08,1.29). PM_{10} was also associated with increased odds of mortality, even though the coefficient was attenuated (OR=1.02, 95% CI:0.91,1.14) as compared to those from the multiple regression model. Results that considered alternative trimming are shown in eTable 6 and indicate no discrepancies with the main finding.

Discussion

In this study, conducted on a large sample of individuals from the Dutch general population, we observed positive associations between air pollution mixtures and all-cause mortality, with $PM_{2.5}$ being the main driver of the associations. Through the application of causal modeling approaches for environmental mixtures, we strengthened the causal interpretation of these findings, observing a strong effect of $PM_{2.5}$ and a moderate effect of PM_{10}.
Our findings are in line with results from previous studies (Cohen et al., 2017; Pinault et al., 2016; Strak et al., 2021), with the Netherlands being characterized by homogeneous geographic conditions due to its relatively small land extension and high population density compared to other geographic areas around the globe. In this regard, a recent systematic review supporting the derivation of updated guidelines by the World Health Organization (WHO) on PM exposure and mortality, highlighted the importance of considering the heterogeneity of study location and population characteristics, as well as level and composition of PM, among others, when interpreting and comparing results from different studies (Chen & Hoek, 2020).
The potential harmful effects of air pollution on overall mortality have been the primary focus of extensive research over the last decades (Brook et al., 2010; Di et al., 2017; Wei et al., 2021; *World Health Organization. Ambient (Outdoor) Air Quality and Health. Fact Sheet No. 313. Geneva: World Health Organization.*, 2015). Associations have been repeatedly observed all over the world, and recent studies have also suggested that associations might follow linear relationships where even low levels of pollution might be harmful for health (Di et al., 2017; Shi et al., 2016; Strak et al., 2021). Nevertheless,

several research gaps in air pollution epidemiology remain to be addressed. First, air pollution is a complex exposure that should be characterized as a mixture, with different components and constituents possibly operating through either similar or different biologic pathways in the human body (Austin et al., 2012; Gass et al., 2014; Pearce et al., 2014, 2015; Winquist et al., 2014; Zanobetti et al., 2014). Extensive work has been devoted to the development of high-resolution concentration surfaces of the different components and constituents of the complex ambient air pollution exposure (Bellavia et al., 2021; Carrico et al., 2015; Greifer, 2017; Hirano & Imbens, 2005; Imai & Dyk, 2004; Lampa et al., 2014; Rosenbaum & Rubin, 1983; Williams & Crespi, 2020). Epidemiologic studies, however, are mostly evaluating air pollution components one by one, and switching the focus to air pollution as an environmental mixture has been advocated (Dominici et al., 2010b). Second, to improve our understanding of the mechanisms through which air pollution operates and to allow the development of more stringent public health regulations and interventions, it is important to determine to which extent these associations reflect causal relationships (*HEI Health Effect Institute. Strategic Plan for Understanding the Health Effects of Air Pollution. 2020–2025. Fist Draft May 2019. Available Online: Https://Www.Healtheffects.Org/Sites/Default/Files/First-Draft-HEI-StrategicPlan2020-2025.Pdf*, 2019). Methods to address causality in observational studies are widely available (Rothman & Greenland, 2005; Vandenbroucke et al., 2016), and several reports have discussed the application of these techniques in air pollution epidemiology (Carone et al., 2020; Dominici & Zigler, 2017). It is also desirable that such causal modeling approaches will account for the complex nature of air pollution as a mixture (Carone et al., 2020; Dominici & Zigler, 2017).

To the best of our knowledge, this study was one of the first attempts to assess the causal effects of a mixture of air pollutants in a large population-based study. Our results confirm previous findings observed in this and other cohorts, showing a positive linear association between pollution components such as $PM_{2.5}$ and PM_{10} and overall mortality. In addition, by jointly evaluating several components in the same statistical framework, we observed that $PM_{2.5}$ seems to be the strongest predictor of overall mortality, and that interactive mechanisms were not influential in our cohort. The possible mechanisms through which $PM_{2.5}$ operates are increased systemic inflammation and oxidative stress, increased blood pressure, and reduced lung function, thus resulting in a greater risk of cardiovascular and respiratory morbidity (Shi et al., 2016). Results are consistent across the different methods applied, with the largest effect on overall mortality obtained for $PM_{2.5}$ using the multivariate generalized propensity score. This method possibly provides, on theoretical grounds, more robust estimates compared to both the univariable and multivariable logistic regression, and the univariate generalized propensity score. However, due to the lack of studies that have previously applied this extension of the propensity score in epidemiologic settings, and therefore the inability to directly com-

pare our findings with those obtained in other cohorts, this result must be interpreted with caution. The 2019 Integrated Science Assessment (ISA) released by US Environmental Protection Agency (EPA) rated the association between $PM_{2.5}$ and natural-cause mortality as suggestive (EPA, n.d.), contrary to PM_{10} which was already fully recognized as harmful to human health. Our results, by distinguishing the roles of PM_{10} and $PM_{2.5}$, and showing the prominent role of the latter in our study population, provide relevant results that can inform future public health policies.

This study has several strengths. First, it is one of the first studies to evaluate the causal effects of air pollution while jointly evaluating several pollutants components as an environmental mixture. Specifically, we used a recent extension of the generalized propensity score, the multivariate generalized propensity score approach, that, to our knowledge, has never been used before in environmental epidemiology. While making the assumption that all evaluated exposures are normally distributed, the multivariate score improves on several aspects as compared to other approaches. First, the propensity score is a balancing score, which means that conditioning on propensity score via regression adjustment implies that individuals within the same strata of the propensity score should be identical in terms of their observable characteristics, regardless of their level of treatment (Hirano & Imbens, 2005; Imai & Dyk, 2004). Thanks to the balancing property, the propensity score thus removes sources of potential confounding and returns valid estimates by balancing covariates to predict the probability of exposure (Rosenbaum & Rubin, 1983). Second, the multivariate generalized propensity score approach has the ability of simultaneously estimating propensity score weights for each exposure, thus achieving superior balance compared to univariate alternatives. In addition, through the multivariate score it is possible to specify multiple sets of confounders for each exposure of interest reflecting many real-world settings in which the confounders may actually differ across exposure variables. Finally, the option to trim extreme weights at a particular percentile, and the wide number of metrics that can be used to select and compare different propensity score approaches, make the multivariate generalized propensity score a method well suited to get more robust estimates on the joint effect of multiple continuous exposures on health outcomes, confirming and possibly strengthening results obtained with more traditional methods. We recommend that future studies validate our results in other cohorts with this or alternative causal modeling techniques.

Second, we used a pluralistic approach integrating several statistical methods for causal inference and environmental mixtures (Vandenbroucke et al., 2016). To identify relevant predictors within the air pollution mixture we used two statistical methods, namely weighted quantile sum and boosted regression tree, that allow ranking the importance of exposures in the overall mixture–outcome association, thus informing which regression results might be biased due to the high correlation. In this study, multiple regression results were influenced by (multi)collinearity due to the high correlation structure, par-

ticularly $PM_{2.5}$absorbance which was shown to be mostly irrelevant in the mixture–outcome association once the high correlation was accounted for. Third, we used data from a large population of Dutch individuals with a prospective design, and a high-resolution assessment of air pollution components, all elements that further enhance the robustness of our results and the causal interpretation of these findings.

A limitation of this study is the relatively short duration of follow-up that did not allow us to thoroughly evaluate how effects of air pollution may change over time. Future studies with longer follow-up should replicate these analyses and evaluate overall mortality as a time-to-event outcome for those statistical techniques where this extension is available. Moreover, no information was available on air pollution levels other than those modeled at the participants' home address, thus precluding the possibility to quantify the exposure in places where participants could have spent some of their time during the day or when moving from one place to another. Furthermore, information on emigration time was not available for the majority of participants who had emigrated during the follow-up. As such, these individuals had to be excluded from the analysis. In addition, despite several socio-demographic covariates that were available and could be investigated as potential confounders of the associations, we cannot exclude the presence of residual confounding due to variables that were not available in this study. Exposures were derived using land-use regression models, which might introduce more complexity due to the use of shared predictors that may lead to stronger correlations between exposures than those existing in the real world (Szpiro & Paciorek, 2013). In large cohorts as the one we considered in our study, it is usually difficult or impossible to directly measure the different pollutants for each participant due to logistics complexity and the high costs associated, and therefore it is common to rely on exposure modeling. This is also suggested by WHO which indicates that exposure modeling is a logical or empirical construct which allows estimation of individual or population exposure parameters from available input data (World Health Organization. Regional Office for Europe, 2000). Finally, in this first attempt to evaluate the causal effects of air pollution mixture we only focused on five major components of air pollution that had been assessed in this cohort. Future studies within LIFEWORK should consider finer pollution characterization, once this is available, by integrating additional components into the models, such as ultrafine particles, black carbon, as well as PM elemental constituents. Also, future studies could further expand analyses to include additional environmental risk factors (water pollution, noise, electromagnetic fields) and relevant conditions, such as lung cancer or respiratory diseases, making use of the statistical methods we proposed in our study to account for complex interrelations between risk factors in real-life settings. These results should also advise quantitative researchers to study and develop novel methods that could improve our understanding of the causal effects of complex mixtures of environmental pollutants.

Conclusions

In conclusion, this study strengthened the causal interpretation of air pollution effects on mortality while also accounting for the complex nature of the exposure as an environmental mixture. We encourage air pollution researchers to further study the causal effects of air pollution mixtures to continue improving our scientific knowledge on the relationship between air pollution and health outcomes, and to facilitate governmental bodies to better target regulations thanks to the identification of the strongest contributor(s) to overall mortality from a complex mixture.

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Table 1. Baseline characteristics of the LIFEWORK participants and estimated annual pollutant exposures[a] at subject recruitment, overall and by levels of pollution exposure[b].

	Low exposure (N=34,018)	Moderate exposure (N=37,853)	High exposure (N=15,011)	Overall (N=86,882)
No. of participants (%)				
Amigo	22	15	10	17
EPIC	9	16	28	15
Nightingale	69	69	62	68
Age (years)				
Mean (SD)	48.8 (11.6)	50.5 (12.9)	52.2 (14.3)	50.2 (12.7)
Sex (%)				
Male	12	9	9	11
Female	88	91	91	89
Highest level of education attained[c] (%)				
Low	11	14	18	14
Intermediate	48	43	35	44
High	41	43	47	42
Missing	0.2	0.2	0.3	0.2
Smoking status (%)				
Never	48	47	44	46
Former	40	40	40	40
Current	11	12	14	13
Missing	0.6	1.0	1.7	1.0
Body mass index (kg/m^2)				
Mean (SD)	25.2 (4.16)	25.3 (4.30)	25.2 (4.41)	25.3 (4.26)
Missing (%)	0.4	0.6	0.9	0.6
CVD diagnosis at baseline (%)				
Negative	93	93	90	92
Positive	7	7	10	8
COPD diagnosis at baseline (%)				
Negative	98	97	96	97
Positive	2	3	4	3
Cancer diagnosis at baseline (%)				
Negative	98	97	95	97
Positive	2	3	5	3
Monthly income estimate[d]				
Mean (SD)	2,590 (764)	2,800 (890)	2,870 (1,000)	2,730 (873)
Missing (%)	5.1	3.4	3.3	4.0
Normalized difference vegetation index				

Mean (SD)	0.571 (0.0844)	0.503 (0.0796)	0.448 (0.0864)	0.520 (0.0943)
Missing (%)	2.6	1.2	0.9	1.7
NO_2 ($\mu g/m^3$)				
Mean (SD)	17.7 (2.55)	24.9 (2.25)	33.7 (4.30)	23.6 (6.34)
$PM_{2.5}$ ($\mu g/m^3$)				
Mean (SD)	16.3 (0.721)	16.7 (0.559)	17.0 (0.707)	16.6 (0.704)
$PM_{2.5}$ absorbance (10^{-5} m^{-1})				
Mean (SD)	1.09 (0.132)	1.29 (0.125)	1.57 (0.227)	1.26 (0.225)
PM_{10} ($\mu g/m^3$)				
Mean (SD)	24.1 (0.381)	24.7 (0.643)	26.4 (1.42)	24.8 (1.12)
Oxidative Potential (nmol DTT/min/m^3)				
Mean (SD)	1.06 (0.208)	1.22 (0.165)	1.32 (0.119)	1.17 (0.202)

[a]Air pollution levels were estimated at baseline based on annual average concentrations measured between October 2008 and April 2011 (NO_2, $PM_{2.5}$, $PM_{2.5}$ absorbance, PM_{10}) and between February 2009 and February 2010 (Oxidative Potential).
[b]Low, medium, and high levels of exposures derived with cluster analysis.
[c]Low: primary school, lower vocational training or lower secondary education; intermediate: intermediate vocational education or intermediate/higher secondary education; high: higher vocational education or university degree.
[d]Household income was estimated based on participants' baseline postal code. Each postal code was linked to income data from Statistics Netherlands for December 2012.
CVD=cardiovascular disease; COPD=chronic obstructive pulmonary disease; SD=standard deviation.

Table 2. Odds Ratios of overall mortality per interquartile range width increase in mean air pollution exposure, evaluated with a multivariable logistic regression model.

	Multivariable model with minimal adjustment[a]		
Constituent	OR	95%CI	VIF
NO_2	0.98	(0.82;1.18)	5.11
$PM_{2.5}$	1.17	(0.99;1.37)	4.03
$PM_{2.5}$ absorbance	0.74	(0.55;0.98)	18.60
PM_{10}	1.21	(1.03;1.42)	7.22
Oxidative Potential	1.07	(0.96;1.19)	1.58

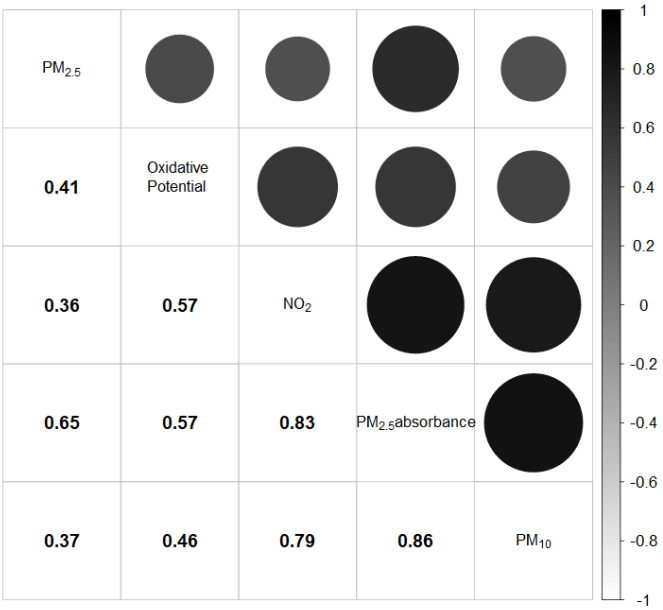
[a]Age, sex, BMI, smoking, CVD diagnosis.
BMI=body mass index; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; VIF=variance inflation factor.

Table 3. Odds Ratios of overall mortality per interquartile range width increase in mean air pollution exposure, evaluated with univariate and multivariate generalized propensity score[a] models [b].

	GPS		mvGPS	
Constituent	OR	95%CI	OR	95%CI
NO_2	1.10	(1.01;1.19)	1.13	(0.97;1.31)
$PM_{2.5}$	1.11	(1.03;1.20)	1.18	(1.08;1.29)
PM_{10}	1.08	(1.02;1.15)	1.02	(0.91;1.14)
Oxidative Potential	1.09	(1.00;1.19)	0.97	(0.89;1.06)

[a]Trimming 0.99.
[b]PS based on age, sex, BMI, smoking, CVD diagnosis.
BMI=body mass index; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; GPS=generalized propensity score; mvGPS=multivariate generalized propensity score.

Figure 1. Spearman rank correlation coefficients and correlation plot of air pollution constituents at baseline (2008-2011). Darker colors and larger circles indicate higher positive correlation levels.



SUPPLEMENTARY MATERIAL

Title: A multi-pollutant approach to estimating causal effects of air pollution mixtures on overall mortality in a large, prospective cohort

Authors: Eugenio Traini[1], Anke Huss[1], Lützen Portengen[1], Matti Rookus[2], W.M. Monique Verschuren[3,4], Roel Vermeulen[1], Andrea Bellavia[1,5]

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Supplementary Table 1. Distribution of the estimated annual pollutant exposures at baseline in LIFEWORK.

	Minimum	25th Percentile	Median	Mean	75th percentile	Maximum
NO_2 (μg/m^3)	8.87	19.07	22.92	23.59	27.34	88.72
$PM_{2.5}$ (μg/m^3)	14.86	16.17	16.56	16.58	17.04	21.33
$PM_{2.5}$ absorbance (10^{-5} m^{-1})	0.85	1.12	1.23	1.26	1.37	3.16
PM_{10} (μg/m^3)	23.73	23.96	24.44	24.77	25.15	34.54
Oxidative Potential (nmol DTT/min/m^3)	0.48	1.04	1.19	1.17	1.31	2.09

Supplementary Table 2. Odds Ratios of overall mortality per interquartile range width increase in mean air pollution exposure, evaluated with univariable and multivariable logistic regression models.

	Univariable models with minimal adjustment[a]		Multivariable model with full adjustment[b]		
Constituent	OR	95%CI	OR	95%CI	VIF
NO_2	0.98	(0.90;1.07)	0.93	(0.77;1.13)	5.30
$PM_{2.5}$	1.04	(0.95;1.12)	1.12	(0.95;1.32)	4.04
$PM_{2.5}$ absorbance	1.00	(0.93;1.07)	0.80	(0.59;1.08)	18.59
PM_{10}	1.01	(0.95;1.08)	1.17	(0.99;1.38)	7.21
Oxidative Potential	1.03	(0.94;1.12)	1.04	(0.93;1.17)	1.85

[a]Age, sex, BMI, smoking, CVD diagnosis.
[b]Age, sex, BMI, smoking, CVD diagnosis, COPD diagnosis, cancer diagnosis, education, income, normalized difference vegetation index.
BMI=body mass index; CVD=cardiovascular disease; COPD=chronic obstructive pulmonary disease; OR=odds ratio; CI=confidence interval; VIF=-variance inflation factor.

Supplementary Table 3. Odds Ratios of overall mortality per interquartile range width increase in mean air pollution exposure, evaluated with a multivariable logistic regression model using multiple imputation by chained equations for missing values in the exposures.

	Multivariable model with minimal adjustment[a]		
Constituent	OR	95%CI	VIF
NO_2	0.98	(0.82;1.17)	5.11
$PM_{2.5}$	1.17	(0.99;1.37)	4.03
$PM_{2.5}$ absorbance	0.74	(0.55;0.98)	18.61
PM_{10}	1.21	(1.04;1.42)	7.23
Oxidative Potential	1.07	(0.96;1.19)	1.58

[a]Age, sex, BMI, smoking, CVD diagnosis.
BMI=body mass index; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; VIF=variance inflation factor.

Supplementary Table 4. Odds Ratios of overall mortality per interquartile range width increase in mean air pollution exposure in a subset of constituents, evaluated with a multivariable logistic regression model.

	Multivariable model with minimal adjustment[a]		
Constituent	OR	95%CI	VIF
NO_2	0.91	(0.79;1.04)	2.85
$PM_{2.5}$	1.03	(0.94;1.14)	1.37
PM_{10}	1.06	(0.95;1.17)	3.10

[a]Age, sex, BMI, smoking, CVD diagnosis.
BMI=body mass index; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; VIF=variance inflation factor.

Supplementary Table 5. Hazard Ratios of overall mortality per interquartile range width increase in mean air pollution exposure, evaluated with a Cox proportional hazards regression model.

	Cox model with minimal adjustment[a]	
Constituent	HR	95%CI
NO_2	1.00	(0.83;1.20)
$PM_{2.5}$	1.19	(1.02;1.39)
$PM_{2.5}$ absorbance	0.73	(0.55;0.96)
PM_{10}	1.22	(1.05;1.43)
Oxidative Potential	1.07	(0.97;1.19)

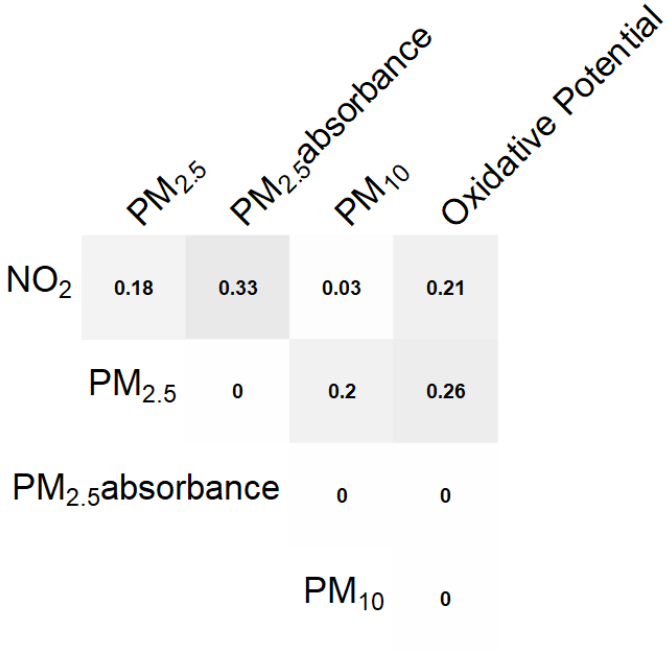
aAge, sex, BMI, smoking, CVD diagnosis.
BMI=body mass index; CVD=cardiovascular disease; HR=hazard ratio; CI=confidence interval.

Supplementary Table 6. Odds Ratios of overall mortality per interquartile range width increase in mean air pollution exposure, evaluated with univariate and multivariate generalized propensity score models[a] with varying trimming thresholds.

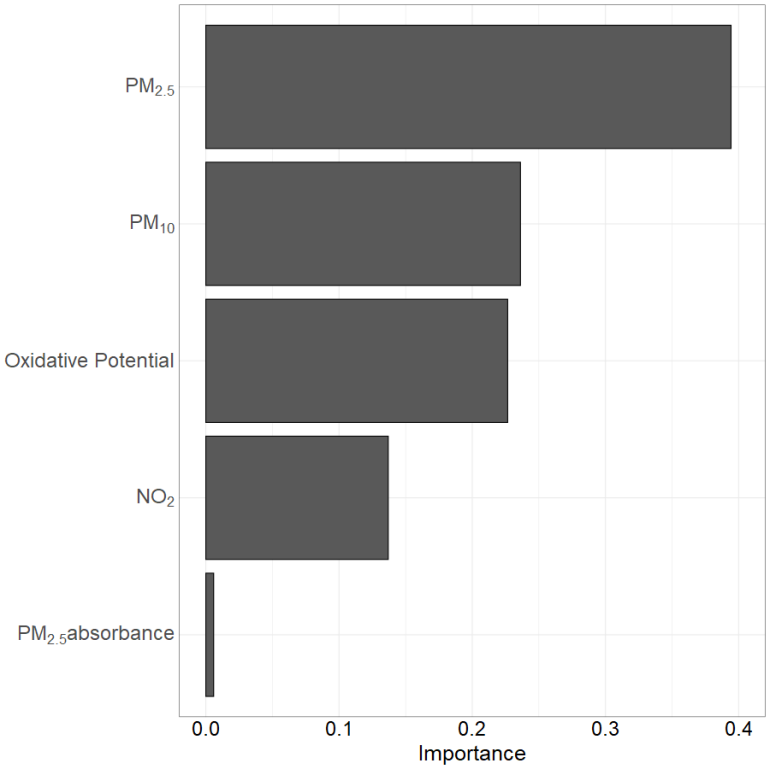
	GPS		mvGPS	
Constituent	OR	95%CI	OR	95%CI
Trimming=0.97				
NO_2	1.12	(1.03;1.21)	1.16	(0.99;1.36)
$PM_{2.5}$	1.13	(1.04;1.21)	1.08	(0.99;1.19)
PM_{10}	1.10	(1.04;1.17)	1.01	(0.90;1.14)
Oxidative Potential	1.10	(1.01;1.20)	1.01	(0.92;1.11)
Trimming=0.95				
NO_2	1.13	(1.04;1.22)	1.16	(0.99;1.36)
$PM_{2.5}$	1.13	(1.05;1.22)	1.08	(0.98;1.18)
PM_{10}	1.11	(1.05;1.18)	1.00	(0.88;1.13)
Oxidative Potential	1.11	(1.02;1.21)	1.00	(0.90;1.10)

[a]PS based on Age, sex, BMI, smoking, CVD diagnosis.
BMI=body mass index; CVD=cardiovascular disease; OR=odds ratio; CI=confidence interval; GPS=generalized propensity score; mvGPS=multivariate generalized propensity score

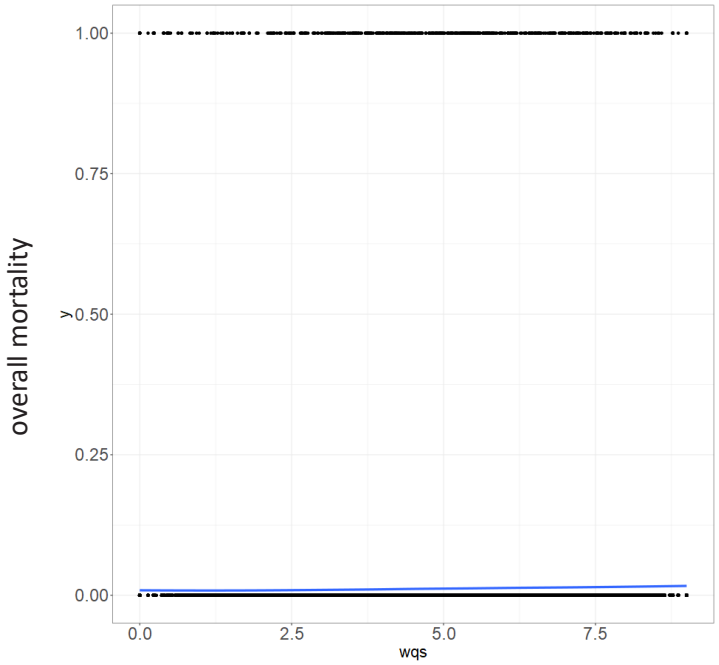
Supplementary Figure 1. Relevance of 2-way interactions (H-statistics) in the overall mixture effect in predicting overall mortality, estimated with boosted regression tree.

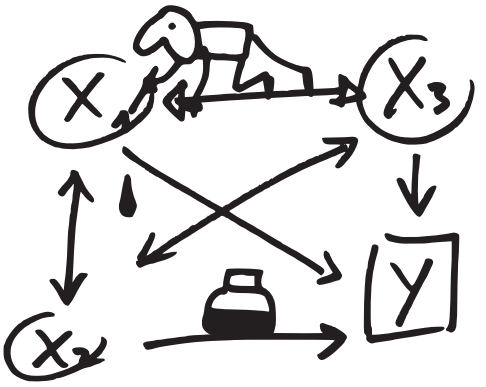


Supplementary Figure 2. Relative importance of mixture components in the overall effect of air pollution on overall mortality, estimated with weighted quantile sum.



Supplementary Figure 3. Association between the mixture and overall mortality, estimated with weighted quantile sum.




X1
X3
Y
X2

Chapter 5: A prospective exploration of the urban exposome in relation to headache in the Dutch population-based Occupational and Environmental Health Cohort Study (AMIGO)

Authors: Eugenio Traini[1], Lützen Portengen[1], Haykanush Ohanyan[1], Robert van Vorstenbosch[1], Roel Vermeulen[1], Anke Huss[1]

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Abstract

Objective: Headache is one of the most prevalent and disabling health conditions globally. We prospectively explored the urban exposome in relation to weekly occurrence of headache episodes using data from the Dutch population-based Occupational and Environmental Health Cohort Study (AMIGO).

Material and Methods: Participants (N=7,339) completed baseline and follow-up questionnaires in 2011 and 2015, reporting headache frequency. Information on the urban exposome covered 80 exposures across 10 domains, such as air pollution, electromagnetic fields, and lifestyle and socio-demographic characteristics. We first identified all relevant exposures using the Boruta algorithm and then, for each exposure separately, we estimated the average treatment effect (ATE) and related standard error (SE) by training causal forests adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly occurrence of headache episodes at baseline.

Results: Occurrence of weekly headache was 12.5% at baseline and 11.1% at follow-up. Boruta selected five air pollutants (NO_2, NO_X, PM_{10}, silicon in PM_{10}, iron in $PM_{2.5}$) and one urban temperature measure (heat island effect) as factors contributing to the occurrence of weekly headache episodes at follow-up. The estimated causal effect of each exposure on weekly headache indicated positive associations. NO_2 showed the largest effect (ATE=0.007 per interquartile range (IQR) increase; SE=0.004), followed by PM_{10} (ATE=0.006 per IQR increase; SE=0.004), heat island effect (ATE=0.006 per one-degree Celsius increase; SE=0.007), NO_x (ATE=0.004 per IQR increase; SE=0.004), iron in PM2.5 (ATE=0.003 per IQR increase; SE=0.004), and silicon in PM_{10} (ATE=0.003 per IQR increase; SE=0.004).

Conclusion: Our results suggested that exposure to air pollution and heat island effects contributed to the reporting of weekly headache episodes in the study population.

Introduction

Headache disorders, characterized by their diverse intensity and frequency, represent one of the most prevalent and incapacitating health conditions globally (GBD 2016 Headache Collaborators, 2018; Steiner & World Headache Alliance, 2004).

While genetic factors have been acknowledged to play a role in the onset of headaches (Di Lorenzo et al., 2015; Russell et al., 2006), emerging research emphasizes the substantial impact of lifestyle and behavioral characteristics as well as environmental factors on the initiation and persistence of headaches (Friedman & De Ver Dye, 2009; Molarius et al., 2008; Ulrich et al., 2004). As such, no single factor can be considered the sole trigger of headaches in the population; rather, their occurrence is likely the result of a combination of various factors including, among others, stress, lack of sleep, diet, analgesic overuse, environmental stressors, and urban temperature (Ashina et al., 2023; Holzhammer & Wöber, 2006; M. Lee et al., 2018; Nash & Thebarge, 2006; Nikiforow & Hokkanen, 1978; Prince et al., 2004; Rains & Poceta, 2012; Raucci et al., 2021; Winter et al., 2011). For instance, exposure to high levels of air pollution has been associated with an increased risk of hospitalization for headache (Dales et al., 2009). Similarly, exposure to specific chemicals, such as metals, has been suggested to increase headache susceptibility (Donma & Donma, 2002).

As we explore the impact of lifestyle factors, behavioral characteristics, and environmental stressors on headaches, it becomes evident that their intricate dynamics require a comprehensive understanding to inform targeted interventions and personalized approaches to headache management that cannot be achieved by considering each factor separately. The exposome is defined as the totality of exposures that individuals encounter over their lifetimes and the biological reactions that these stressors produce (Vermeulen et al., 2020; Wild, 2005). As such, the urban exposome denotes a complex interplay between the built, social, chemical, food, and lifestyle aspects of the environment where people live. This interaction is characterized by persistent spatial and temporal variations in both quantitative and qualitative measures associated with different aspects of residential surroundings, and, as a consequence, these fluctuations may impact the well-being and health of individuals (Andrianou & Makris, 2018).

To the best of our knowledge, the relationship between urban exposome and headache has not yet been explored. In this study, we aimed to prospectively evaluate factors related to reporting of weekly headache episodes, in a large study population relying on the exposome framework. We conducted an exploratory analysis using data from the urban exposome of the Dutch population-based Occupational and Environmental Health Cohort Study (AMIGO), which represents a rich dataset comprising detailed individual-level information on various determinants (e.g. chemical, biological, physical), lifestyle factors, and health conditions for over 14,000 participants.

Methods

Study design and participants

We used data from the population-based Occupational and Environmental Health Cohort Study (AMIGO) in the Netherlands, established in 2011/2012 to investigate environmental and occupational determinants of diseases and symptoms in the Dutch adult population. The rationale, study design, and participant recruitment in AMIGO were described in detail previously (Slottje et al., 2014). In short, AMIGO participants were recruited from the general population in the Netherlands through the Primary Care Database of the Netherlands Institute for Health Services Research (NIVEL), which consists of routinely recorded data from health care providers to monitor health and utilization of health services in the Dutch population (*Nivel Primary Care Database | Nivel*, 2022). The baseline sample includes 14,829 adults (16% of those invited), aged 31–65 years, who filled in an online questionnaire in 2011/2012 and at follow-up in 2015 (n=7,905; response rate 54%). After the exclusion of participants with missing information on headache frequency at baseline and/or follow-up (n=566), the study population included 7,339 participants who completed baseline and follow-up questionnaires. All cohort members participated voluntarily and gave informed consent prior to their inclusion.

Exposure factors

The urban exposome of AMIGO was described by Ohanyan et al. previously (Ohanyan, Portengen, Huss, et al., 2022). In short, the urban exposome relied on satellite data, monitoring stations, population registry-based data, and geospatial models to estimate participants' exposures at their place of residence at baseline (Martens et al., 2018). In this study, 88 exposures across 10 domains were considered encompassing air pollution (19 factors), quality of drinking water (29 factors), urbanicity and built environment (13 factors), green space density (2 factors), outdoor light at night (1 factor), urban temperature (2 factors), road traffic noise (1 factor), radiofrequency electromagnetic fields (2 factors), socio-demographic characteristics of the neighborhood (17 factors), technology use (2 factors). The list of exposure factors included in this study is provided in Supplementary Table 1.

Headache

Frequency of headache was self-reported at baseline and follow-up. As primary outcome, we defined the occurrence of weekly headache episodes (referred to as "weekly headache" for brevity, with response categories "yes", "no") according to the question: "How often do you get headache at the moment?" - response categories: "almost every day", "5 or 6 days a week", "3–4 days a week", "once or twice a week" "1–2 days per month", "less often".

As secondary outcome, we included the occurrence of severe weekly headache episodes

(response categories “yes”, “no”). The Headache Impact Test (HIT-6) score with a cut-off of 56 points was used to define weekly occurrence of severe headache episodes. The HIT-6 is a tool used to measure the impact headaches have on one’s ability to function in various aspects of daily life, including work, school, home, and social contexts. The score, ranging from 36 to 78 points, provides a measure of the degree to which headaches affect daily life and functioning, with higher scores indicating a more significant impact on the participant’s overall life (Kosinski et al., 2003).

Covariates

We assessed the following covariates of the associations between the urban exposome and weekly headache: sex, age, highest level of education attained (elementary, secondary and higher), occupation (employed, unemployed), country of origin (the Netherlands, other), body mass index (BMI) group (normal or underweight, overweight or obese), alcohol consumption (never, former, current), smoking status (never, former, current), sleep disturbance index (Spritzer & Hays, 2003), general health indicator (good, poor), depression diagnosis (yes, no), painkiller use (yes, no).

Pre-processing of the urban exposome and descriptive statistics

We followed the same approach outlined by Ohanyan et al. to pre-process the urban exposome data in AMIGO (Ohanyan, Portengen, Kaplani, et al., 2022). In short, we excluded exposures that exhibited extremely low variability (9 exposures) or very strong correlations with other exposures (7 exposures). In the latter scenario, where two (or more) exposures showed a Spearman rank correlation coefficient ≥ 0.95, only one of the correlated variables was incorporated into the analysis and treated as a proxy for the other variable(s) (Supplementary Table 2).

Missing values were imputed for exposures and covariates only, and all exposures, covariates, and the study outcome were used as predictors. Thirty imputed datasets were generated through Multivariate Imputation via Chained Equations (MICE) and the imputed values were averaged across the generated datasets, given the considerable computational costs and the absence of a recognized approach to combine results from multiple imputed sets associated with the methods applied in this study.

To mitigate the potential impact of non-normal distribution of the exposures on the imputation process, we applied transformations (logarithmic or square root) to normalize the exposures before incorporating them into MICE, and then back-transformed them after the imputation (Buuren & Groothuis-Oudshoorn, 2011; White et al., 2011).

Descriptive statistics of the study population were evaluated with regard to the covariates included in the study. We performed a correlation analysis of the urban exposome by visualizing the inter- and intra-group correlations across the 10 domains using the circos and matrix of correlations, respectively (Hernandez-Ferrer et al., 2022).

Statistical analysis

To evaluate the association between the urban exposome at baseline and weekly occurrence of headache episodes at follow-up, we first performed feature selection using the Boruta algorithm to screen our dataset and identify relevant exposures for the outcome being investigated (Kursa & Rudnicki, 2010).

Boruta represents a powerful approach for the analysis of high-dimensional datasets that has recently gained popularity particularly in the context of microbiome and omics research (Degenhardt et al., 2017). This method is designed to identify relevant variables and is able to capture interactions and nonlinear associations in complex-dimensional scenarios. Boruta aims to identify all attributes that contribute to some extent to the classification problem based on the so-called *all-relevant* problem approach. This methodology stands in contrast to the *minimal-optimal* problem approach, which focuses on finding the smallest and non-redundant subset of features essential for optimal performance given a specific dataset (Nilsson et al., 2007).

Boruta works as a wrapper algorithm around random forest and operates by comparing the importance of each variable against that of shadow variables, which are randomly permuted versions of the original variables (Breiman, 2001; Liaw & Wiener, 2002). By conducting a series of random forest iterations, Boruta assigns importance scores to each variable, considering both the actual features and their shadow counterparts. Variables that consistently outperform their shadow versions are retained as important, while those that do not are deemed unimportant.

To address class imbalance, we applied the Boruta algorithm repeatedly (250 iterations using 1000 trees at each iteration) and downsampled 85% of the minority group size without replacement in both groups comprising participants with and without weekly headaches at follow-up in order to obtain 250 different balanced datasets (More & Rana, 2017).

Finally, we retained the features that were labelled as “important” by Boruta in at least 80% of the 250 iterations, emphasizing their stability in the selection process, and calculated variable importance by averaging the importance of the selected features across iterations.

To evaluate the generalizability of our results, we trained a random forest model on the features selected by Boruta. This evaluation was conducted on an *a priori* sampled independent test set, comprising 20% of the original dataset. The corresponding Receiver Operating Characteristics (ROC) curve and Area-Under-the-Curve (AUC), along with a 95% confidence interval (95% CI), were estimated using 1000 bootstrap replicates.

To visualize the relationship between the response and predictors, and represent the average contribution of a feature value to the prediction (Molnar, 2020), we computed Shapley values by training a random forest model on the features identified by Boruta using the original dataset.

We estimated the causal effect of each exposure identified by Boruta on weekly occurrence of headache episodes by training causal forests. Causal forests represent an extension of random forests to estimate the average treatment effect (ATE) and corresponding standard error (SE) under the assumption of absence of confounding (i.e. the treatment assignment is independent of the potential outcome conditional on the confounders) allowing for covariate adjustment. The ATE represents the average of the difference in potential outcomes in a sample where everyone is treated versus the same sample where everyone is untreated (Jawadekar et al., 2023).

Specifically, when the treatment is continuous, we effectively estimate an average partial effect, which quantifies the change in the expected outcome due to a one-unit change in the treatment, given unconfoundedness. To ensure clarity and consistency in the language used, we will refer to treatment as exposure in the rest of the paper.

Briefly, the algorithm splits the data in order to maximize the difference across splits in the relationship between an outcome and an exposure variable uncovering variations in exposure effects across the sample. Causal forests resemble a randomized controlled trial and estimate exposure propensity weights to create a balanced covariate distribution between the exposed and control groups. It is important to note that, while causal forests identify heterogeneity in causal effects, they do not, per se, establish causation (Athey et al., 2018).

In detail, for each exposure selected by Boruta, we estimated causal forests adjusted for a set of covariates. In estimating causal forests, we used default parameters as they were shown to perform reasonably well with random forests (Athey & Wager, 2019).

To assess the fit of the causal forest, we first examined the distribution of the estimated exposure propensity weights to identify potential extreme values. Second, we explored heterogeneity by grouping observations according to whether their out-of-bag conditional average treatment effect (CATE) estimates (i.e. predictions) were above (“high” region) or below (“low” region) the median CATE estimate. Following this grouping, we calculated the difference in causal effects between regions along with the 95% confidence interval (95% CI) to gain insights about the overall strength of heterogeneity in the study population (Athey & Wager, 2019).

As secondary analyses, considering the transient nature of headaches in the population and our predefined interest in assessing whether exposure effects on weekly headaches at follow-up could be mediated by their occurrence at baseline, we trained additional causal forests. Specifically, we estimated the CATE representing the average of the difference in potential outcomes in a specific stratum of the population (here defined by presence/absence of weekly headache at baseline), where everyone in that stratum is exposed versus a scenario where everyone in the same stratum is unexposed (Jawadekar et al., 2023). Finally, to test the null hypothesis of no heterogeneity between the CATEs estimated for the two groups of weekly headache at baseline, we applied

Student's t-test (Athey & Wager, 2019).
We conducted the following sensitivity analyses: first, we estimated causal forests with mutual adjustment under the assumption that the exposures may act as confounding factors for each other and are therefore not independent entities. This approach involved systematically estimating the causal effect of each exposure separately on weekly headache while simultaneously incorporating the remaining exposures into the adjustment set. This iterative process was repeated for each exposure identified by Boruta.
Second, we performed the Boruta feature selection by excluding possible mediators of the association between the urban exposome and weekly headache, namely weekly headache at baseline, general health indicator, sleep disturbance index, and self-reported painkiller use. Third, we replicated the feature selection by adding the perception of environmental factors, such as air pollutants and RF-EMFs, to the list of exposures assessed by Boruta, which may help to disentangle the relationship between actual exposures, their perceptions, and the onset of headache symptoms.
Fourth, we reproduced the Boruta feature selection by excluding participants reporting weekly headache at baseline to assess consistency of determinants of newly reported headaches.
Lastly, based on the results of the sensitivity analyses on Boruta, additional causal forests were trained accordingly.
The analyses were performed with the R statistical software, version 4.0.4, using the packages *mice*, *rexposome*, *Boruta*, *ranger*, and *grf* . Computing code related to all analyses presented is publicly available at https://github.com/eugeniotraini/headache_exposome.

Results

In AMIGO, the occurrence of weekly headache episodes at baseline and follow-up showed similar proportions (12.5% and 11.1%, respectively). However, out of the 814 participants reporting weekly headache at follow-up, only 55% reported such headaches at baseline. At the beginning of the study, 5.4% of participants reported experiencing severe headaches weekly, which decreased to 2% at follow-up.
Baseline characteristics of the study population are presented in Table 1. Over half of the participants in AMIGO were women and mean age was 52 years old at the time of recruitment. Approximately 44% of the participants had attained a high level of education, while 70% were employed. Nearly all participants, specifically 96%, indicated the Netherlands as their country of origin. Around half of the study population (48.7%) was classified as overweight or obese, and the proportion of alcohol users and smokers was 88.9% and 12.3%, respectively.
Overall, individuals in the AMIGO study reported a good state of health (85%), low prevalence of painkiller use (6.6%), and an average sleep disturbance index of 26.5 (on a scale from 0 to 100 with higher scores indicating more sleep disturbances or lower

sleep quality). No relevant differences in the distribution of baseline characteristics of the study participants were observed when including those who did not complete the follow-up questionnaire (Supplementary Table 3). The proportion of missing values in the exposures was below 10% with the highest occurrence observed for the percentage of inhabitants with non-western origins in the neighbourhood (9.7%) (Supplementary Table 4).

The matrix of correlation plot shows that the strongest intra-group correlations were observed between air pollutants, urbanicity and built environmental variables, RF-EMFs, and socio-demographic area-level factors (Figure 1). Drinking water components had the lowest intra-group correlations. The circos of correlation plot showed that green space density exhibited a negative inter-family correlation with air pollutants (Supplementary Figure 1).

Results of the Boruta feature selection showed that five air pollutants (NO_2, NO_X, PM_{10}, Silicon in PM_{10}, Iron in $PM_{2.5}$), one urban temperature measure (heat island effect), five *a priori* defined covariates (age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index), and weekly headache at baseline significantly influenced the reporting of weekly headache at follow-up.

Among those, weekly headache at baseline appeared to be the most important variable, followed by the remaining covariates (with age being the least significant among all selected features). The exposures, listed in descending order of importance, were NO_2, Silicon in PM_{10}, NO_X, Iron in $PM_{2.5}$, PM_{10}, and the heat island effect. Spearman correlation coefficients showed very strong correlations between the exposures selected by Boruta (Figure 2).

The Shapley plots did not show strong associations between the selected environmental exposures (air pollutants and urban temperature measure) and weekly headache, and, on average, the contributions of individual features to the predicted outcome were modest (Figure 3).

Being diagnosed with depression, using painkillers, reporting poor general health, experiencing weekly headaches at baseline, being older, and having difficulty sleeping all showed a substantial impact on reporting weekly headache at follow-up (Supplementary Figure 2).

The ROC analysis of the random forest model including the features selected by Boruta produced an AUC of 0.82 (95% CI: 0.75–0.88), indicating good discriminatory power in distinguishing individuals with and without weekly headache at follow-up in the independent test set.

Results from causal forests adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index, and weekly headache at baseline are presented in Table 2 and showed positive associations between each exposure at baseline and weekly headache at follow-up. In detail, NO_2 showed the largest effect with an ATE of

0.007 (SE=0.004) per interquartile range (IQR) increase, followed by PM_{10} (ATE=0.006 (SE=0.004) per IQR increase), heat island effect (ATE=0.006 (SE=0.007) per 1 C° increase), NO_x (ATE=0.004 (SE=0.004) per IQR increase), Iron in $PM_{2.5}$ (ATE=0.003 (SE=0.004) per IQR increase), and Silicon in PM_{10} (ATE=0.003 (SE=0.004) per IQR increase). Of note, concerning the highly correlated exposures identified during the pre-processing of the urban exposome, the use of causal forests with Copper in $PM_{2.5}$ serving as a proxy for Iron in $PM_{2.5}$, yielded results consistent with the main findings (Supplementary Table 5). After conducting a visual inspection of the distribution of estimated propensity weights, no extreme values were identified (Supplementary Figure 3). The assessment of heterogeneity in causal forests revealed some variation between the regions defined by "high" and "low" CATE estimates, though the strength of heterogeneity appeared to be modest (Supplementary Table 6).

The estimated causal effects conditional on weekly headache at baseline showed distinct patterns between participants who reported symptoms at baseline and those who did not. Specifically, as shown in Table 3, the CATE for participants without weekly headache at baseline was null or negative, whereas the effect observed in those who reported headache at baseline was positive. In detail, the CATE of NO_2 among participants who had weekly headache at baseline was 0.068 (SE=0.027), whereas for those without symptoms was -0.003 (SE=0.004). Similar patterns were displayed for all remaining exposures: the heat island effect showed an effect of 0.058 (SE=0.042) for those who reported weekly headache at baseline, while the effect was null (CATE=0.000 (SE=0.006)) for those without weekly headache at baseline. Likewise, PM_{10} showed an effect of 0.054 (SE=0.027) and 0.000 (SE=0.004) in those with and without weekly headache at baseline, respectively. Positive yet weaker effects were observed among participants who reported weekly headache at baseline for Silicon in PM_{10} (CATE=0.043 (SE=0.027)), NO_x (CATE=0.035 (SE=0.022)), and Iron in $PM_{2.5}$ (CATE=0.013 (SE=0.026)). We rejected the null hypothesis of no heterogeneity between the CATEs estimated for the two groups of weekly headache at baseline for all exposures (Table 3).

Interestingly, causal forests spent, on average, 23% of their splits on weekly headache at baseline, making it the most important variable among those included in the algorithm. Supplementary Table 6 displays the results of the mutually adjusted causal forests, where the exposures selected by Boruta were added to the adjustment set.

The mutually adjusted estimates showed reduced precision and some experienced a change in the direction of the effect. In detail, we estimated an ATE of 0.058 (SE=0.022) for an increase in IQR in NO_2, followed by NO_x (ATE=0.011 (SE=0.018)), and PM_{10} (ATE=0.002 (SE=0.014)).

In contrast to the main results, the ATEs for Iron in $PM_{2.5}$, Silicon in PM_{10}, and heat island effect were negative (ATE=-0.016 (SE=0.010); ATE=-0.045 (SE=0.051); ATE=-0.019 (SE=0.017), respectively) (Supplementary Table 7).

No extreme values were identified in the distribution of exposure propensity weights (Supplementary Figure 4), and the comparison between the regions characterized as "high" and "low" CATE estimates aligned with the main results, indicating the presence of some heterogeneity in the dataset (Supplementary Table 8).

Results from the sensitivity analyses using Boruta were in line with the main findings: specifically, by excluding the possible mediators of the association between the urban exposome and weekly headache at follow-up (weekly headache at baseline, general health indicator, sleep disturbance index, and self-reported painkiller use), Boruta retained, in order of decreasing variable importance, depression diagnosis, NO_2, NO_x, Iron in $PM_{2.5}$, and Silicon in PM_{10}. After including the perception of environmental exposures, Boruta selected two air pollutants, namely PM_{coarse} and Potassium in PM_{10}, and road traffic noise, in addition to the features already identified in the main analysis.

Based on these results, we trained additional causal forests including PM_{coarse}, Potassium in PM_{10}, and road traffic noise as exposures, and age, depression diagnosis, and weekly headache at baseline as adjustment factors. The causal effect associated with PM_{coarse}, Potassium in PM_{10}, and road traffic noise on the reporting of weekly headache was 0.005 (SE=0.004), 0.002 (SE=0.004), 0.008 (SE=0.007), respectively (Supplementary Table 9). After excluding participants with weekly headache at baseline, Boruta only selected depression diagnosis and sleep disturbance index but none of the exposures.

Finally, regarding severe weekly headaches, it was found that five predetermined covariates (age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index) and the presence of severe weekly headache at baseline influenced reporting at follow-up. However, none of the environmental exposures were identified by Boruta as contributing factors.

Discussion

In this study, we prospectively explored the urban exposome with the aim to identify factors associated with reporting of weekly headache episodes by analyzing data from a large cohort of individuals sampled within the Dutch general population.

We applied Boruta, a feature selection algorithm designed to identify relevant variables in complex highly dimensional settings, and causal forests, a statistical method for estimating causal effects of exposures under the assumption of absence of confounding.

Our results consistently showed that, out of 88 factors characterizing the urban exposome, air pollutants and urban temperature measures appeared to contribute most to the reporting of weekly headache at follow-up.

In particular, exposure to NO_2 at baseline was the most important environmental factor identified by Boruta in relation to reporting of weekly headache at follow-up, followed by Silicon in PM_{10}, NO_X, Iron in $PM_{2.5}$, PM_{10}, and the heat island effect. Finally, causal forests estimated the largest effect on the reporting of weekly headache at follow-up for NO_2, PM_{10}, and the heat island effect. While the magnitude of these estimates may

be modest, even minor associations can carry important implications when considering the widespread exposure to air pollution and the higher temperatures in urban areas on population health.

Previous research showed that exposure to air pollution may act as trigger in the onset of headaches in the population (Nattero & Enrico, 1996; Szyszkowicz, 2008; Vodonos et al., 2015). The mechanism by which this occurs, however, is not fully understood. Air pollutants can impact the nervous system by entering through the olfactory and lower respiratory tracts. This process involves the direct initiation of inflammatory processes and the release of cytokines, allowing them to reach the central nervous system, triggering symptoms (Block & Calderón-Garcidueñas, 2009). Previous studies conducted in large urban areas in Canada and China suggested that particularly short-term exposure to NO_2 was associated to an increase in the number of emergency department visits for headaches (Szyszkowicz, 2008; Xu et al., 2023). A study conducted in the urban area of Turin in Italy, exploring the relationship between exposure to air pollutants and meteorological factors in relation to headaches, found that simultaneous exposure to carbon monoxide (CO) and NO_2 increased incidence of headache attacks along with wind velocity which was linked to frequency and severity of episodes (Nattero & Enrico, 1996).

It is noteworthy that, despite extensive research indicating positive associations between migraines and air pollution exposure, and particularly NO_2 (Elser et al., 2021; H. Lee et al., 2018; Portt et al., 2023), exploration of headaches is still limited. In this regard, our study highlights the link between exposure to air pollution and the occurrence of headaches, suggesting that measures aimed at decreasing emissions could be beneficial to reduce the impact of pollutants on symptoms. Furthermore, Iron in $PM_{2.5}$ and Silicon in PM_{10} were linked to reporting of headaches in our study population, although their impact appeared to be less prominent compared to NO_2, PM_{10}, and NO_x. To the best of our knowledge, this is the first study to identify specific fine particulate components in relation to headache, and future research should investigate these associations further to elucidate the contribution of individual components, both independently and in combination, to headache occurrence.

Our results showed that the heat island effect, that is the temperature difference between an urban area and the rural surrounding, was causally related with more frequent weekly headache at follow-up. Previously, the increase in temperature, particularly in densely urban areas and especially during summer heat waves, has been linked to immediate body reactions such as heavy sweating, dehydration, skin rashes, and headaches, among others (Aghamohammadi et al., 2021; Arifwidodo & Chandrasiri, 2020; O'Malley et al., 2015; Tong et al., 2021).

In the urban exposome, we used satellite pictures to estimate the surface temperature on a hot day as urban heat island effect is best assessed during heatwaves. Therefore, the effect that we observed in AMIGO could be partially explained by some residual ur-

banicity effect, which may include air pollutants and green space density.

Given the strong interplay between air pollutants and other environmental determinants assessed in the urban exposome, such as road traffic noise and urban temperature, the effect that we found may have, independently or in conjunction with air pollution exposure, exacerbated the reporting of headache.

In our cohort, about half of the participants who indicated to suffer from headache at baseline did not report the same at follow-up, meaning that headache represents a transient condition in the study population. To explore how the exposures may affect different subgroups of participants, specifically those with and without symptoms at the baseline, and therefore improve our understanding of the potential underlying mechanisms that triggered the symptoms, we estimated causal effects conditional on weekly headache at baseline. Interestingly, the estimated effects appeared to be mediated by weekly headache symptoms at baseline. Moreover, baseline weekly headache emerged as the most important variable in the causal forests. These suggest the potential existence of a vulnerable subpopulation, represented by those reporting symptoms at baseline, that is more susceptible and therefore at a higher risk of adverse health outcomes if exposed to air pollution and heat island effect.

In our study, we identified a subset of exposures from the urban exposome which contributed to the occurrence of headache in the population, and estimated the magnitude of their effect under the assumption of absence of confounding using a combination of state-of-the-art statistical methods that, in part, were previously identified as valid tools to address the complexity of the exposome (Maitre et al., 2022; Ohanyan, Portengen, Huss, et al., 2022).

Results from the main analyses indicated that each exposure at baseline identified by Boruta was positively associated with reporting of headache at follow-up. In the mutually adjusted models, the estimates of the causal effects showed some increase for NO_2 and NO_x but with reduced precision, and the direction of the effects was not always consistent with the main results. Spearman correlation coefficients showed very strong correlations (ranging from 0.60 to 0.89) between the exposures selected by Boruta and included in the causal forests.

In methods that rely on propensity scores to balance covariates between exposed and unexposed, such as causal forests, many issues that arise with traditional regression modelling, such as multicollinearity, should no longer be a threat to validity (Arbour et al., 2014; McMurry et al., 2015).

Based on our results, multicollinearity clearly affected the precision of effect estimates produced by causal forests, given the larger standard error associated with the estimates in the mutually adjusted models.

Furthermore, the balancing property of propensity scores which assumes that, conditional on the propensity score, the distribution of observed covariates is expected to be

similar between the treated and untreated groups, is only true if the propensity scores are relatively well-behaved and no extreme values are present (B. K. Lee et al., 2011). However, following an inspection of the distribution of exposure propensities, this did not appear to be the situation in our analysis.

Our study has strengths: first, to our knowledge, this is the first study conducted within the exposome framework to explore the association between the urban exposome and headache. Given the high prevalence of individuals reporting recurrent or chronic headaches in the population, our study provides important insights into the relationship between environmental stressors that are ubiquitous in urban areas and the occurrence of headache symptoms. Our results aim to support the formulation of more tailored public health interventions targeting air quality improvement and a healthier urban environment in order to reduce the burden of headache in the population.

Second, we used data from a large prospective cohort of Dutch individuals, and detailed information about individual-level exposures, including perceived exposures, and neighborhood characteristics, all elements that strengthen the robustness and facilitate the causal interpretation of our results. With regard to generalizability of the data, compared to the general Dutch population, AMIGO participants consisted of more females and older subjects, although no indications of systematic health-related participation bias based on morbidity and associated lifestyle information such as smoking and medication use was found (Slottje et al., 2014).

Third, we used a combination of cutting-edge statistical techniques, that is Boruta and causal forests, to explore the urban exposome in relation to headache. In particular, causal forests and random forest, upon which Boruta is built, were previously identified as valuable tools to study the complexity characterizing exposome research and show good interpretability of the results (Maitre et al., 2022). Furthermore, training Boruta in iterations, despite being time consuming and computationally intensive, helped mitigate the effects of class imbalance present in our dataset, and ensured stability as well as generalizability of our results. In conclusion, we showed that the combination of statistical methods used in this study represents a robust approach to identify influential predictors, particularly in highly dimensional settings, and generate accurate machine learning models to estimate causal effects (Athey & Wager, 2019; Degenhardt et al., 2017; Kursa & Rudnicki, 2010).

Our study has some limitations: first, weekly headache was self-reported by the participants, which may be prone to recall bias or over/under reporting of symptoms. However, we assessed weekly headache using the validated HIT-6 questionnaire, which is considered a reliable and valid tool for discriminating headache impact in daily life, and it is employed as a screening tool in clinical practice (Kosinski et al., 2003). Furthermore, we evaluated severity of weekly headaches as secondary outcome to further strengthen our findings, although results of this analysis did not lead to the identification of any specific

environmental exposures associated to the outcome, likely due to diminished statistical power and even more problematic class imbalance compared to the primary endpoint.
Second, information on weekly headache was available at baseline and follow-up, and no information was available in between. As a result, the outcome assessment may not precisely capture symptoms occurring between these two time points, especially for a transient condition like headache. In future studies, it would be beneficial to confirm the associations that we found between air pollutants and the urban temperature and headache exploring the dynamics of these associations over time.
Third, the exposures included in the urban exposome of AMIGO, such as the air pollutants, were modeled at the home address of the participants. As a consequence, it was impossible to quantify the exposure levels in places where participants could have spent some of their time during the day or when, for example, commuting between work and home. In fact, in cohorts such as AMIGO, directly measuring exposure levels for the single participant proves impractical due to the large sample size and the high costs associated. As a result, it is common to rely on exposure modeling, such as land-use regression models to estimate air pollution levels, which might introduce additional complexity due to the use of shared predictors that may lead to stronger correlations between exposures than those existing in the real world (Szpiro & Paciorek, 2013). In addition, in our study we did not directly evaluate residential self-selection bias, where the decision to relocate is influenced by various factors such as age, ethnicity, professional or life choices, and socioeconomic status. This dynamic may ultimately result in changes in environmental exposures across different life stages (Saucy et al., 2023). Given the complex interplay of these factors with the exposures assessed in AMIGO, we cannot rule out the possibility of residual bias in our dataset originating from residential self-selection.
Finally, despite recent developments in causal inference methods for multiple exposures (Williams & Crespi, 2020), we acknowledge a substantial gap in statistical methods for estimating the effect of multiple exposures, particularly in situations where these are represented by a combination of continuous and categorical exposures, as is common in the context of the urban exposome, and high correlation levels between exposures are present. Nevertheless, the approach followed in this study allowed us to identify a group of exposures involved in the exposome-outcome association and estimate the direct effect of single exposures on reporting of headache controlling for potential confounding variables to obtain more accurate estimates of causal effects.

Conclusions

Our study indicated that the exposure to environmental stressors, in particular air pollutants and urban heat island effects, contributed to reporting of weekly headache episodes in our population. Given the high global burden associated with headache, understanding the role of environmental factors becomes imperative not only for advancing

our comprehension of the mechanisms generating symptoms but also for formulating effective preventing strategies.

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Table 1. Characteristics of the participants at baseline (N=7339).

Sex, n (%)	
Male	3499 (47.7)
Female	3840 (52.3)
Age (years)	
Mean (SD)	52.3 (9.00)
Highest level of education attained, n (%)	
High	3215 (43.8)
Low	4122 (56.2)
Missing	2 (0.0)
Occupation, n (%)	
Employed	5161 (70.3)
Unemployed	2178 (29.7)
Country of origin, n (%)	
The Netherlands	7048 (96.0)
Other	291 (4.0)
BMI group, n (%)	
Normal or underweight	3763 (51.3)
Overweight or obese	3576 (48.7)
Alcohol consumption, n (%)	
No	813 (11.1)
Yes	6524 (88.9)
Missing	2 (0.0)
Smoking status, n (%)	
No	6437 (87.7)
Yes	900 (12.3)
Missing	2 (0.0)
Sleep disturbance index	
Mean (SD)	26.5 (18.6)
Missing	23 (0.3%)
General health indicator, n (%)	
Poor	1098 (15.0)
Good	6239 (85.0)
Missing	2 (0.0)
Depression diagnosis, n (%)	
No	6587 (89.8)
Yes	752 (10.2)
Painkiller use, n (%)	
No	6773 (92.3)
Yes	484 (6.6)
Missing	82 (1.1)
Weekly headache[a], n (%)	
No	6425 (87.5)
Yes	914 (12.5)
Severe weekly headache[a], n (%)	
No	6940 (94.6)
Yes	399 (5.4)

[a]At baseline.

Table 2. Average treatment effects (ATEs) and related standard errors (SEs) estimated with causal forests for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline.

Exposure	ATE[a] (SE)
NO_2 (μg/m^3)	0.007 (0.004)
PM_{10} (μg/m^3)	0.006 (0.004)
Heat island effect (C◦)	0.006 (0.007)
NO_x (μg/m^3)	0.004 (0.004)
Iron in $PM_{2.5}$ (ng/m^3)	0.003 (0.004)
Silicon in PM_{10} (ng/m^3)	0.003 (0.004)

[a]Results for air pollutants indicate changes per interquartile range (IQR) increase in mean air pollution exposure.

Table 3. Conditional average treatment effects (CATEs) on weekly headache at baseline and related standard errors (SEs) estimated with causal forests for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, and sleep disturbance index.

Exposure	CATE[a] (SE) in the subsample of participants with weekly headache at baseline	CATE[a] (SE) in the subsample of participants without weekly headache at baseline	t-value[b]
NO_2 (μg/m³)	0.068 (0.027)	-0.003 (0.004)	7.151***
PM_{10} (μg/m³)	0.054 (0.027)	0.000 (0.004)	6.761***
Heat island effect (C◦)	0.058 (0.042)	0.000 (0.006)	7.645***
NO_x (μg/m³)	0.035 (0.022)	-0.004 (0.004)	4.471***
Iron in $PM_{2.5}$ (ng/m³)	0.013 (0.026)	-0.001 (0.004)	6.209***
Silicon in PM_{10} (ng/m³)	0.043 (0.027)	-0.003 (0.004)	3.916***

[a]Results for air pollutants indicate changes per interquartile range (IQR) increase in mean air pollution exposure.
[b]Null hypothesis of no heterogeneity.
*** p<0.001, ** p<0.01, * p<0.05

Figure 1. Matrix of correlation plot showing the intra-family correlations between exposures at baseline.

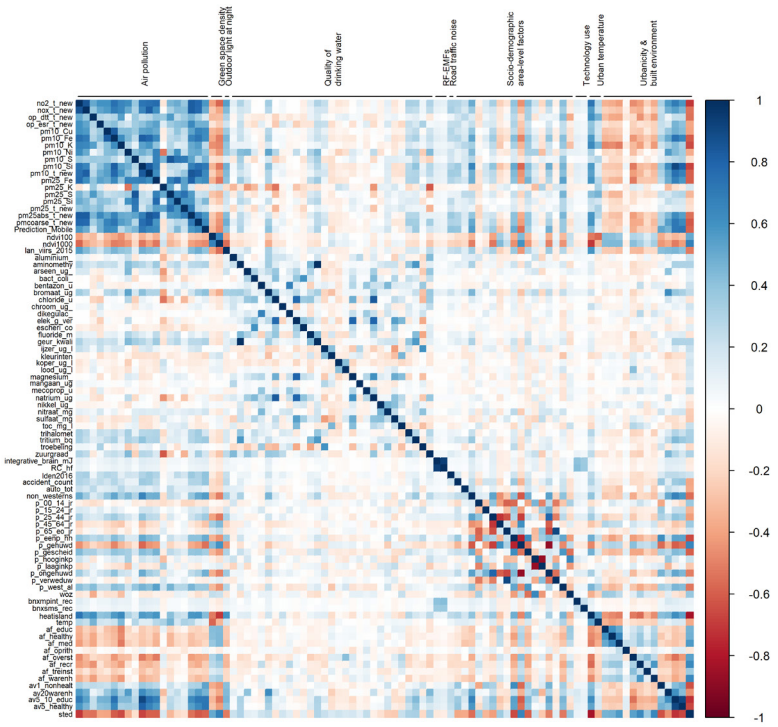


Figure 2. Spearman rank correlation coefficients and correlation plot of the exposures selected by Boruta. Darker colours and larger circles indicate higher positive correlation levels.

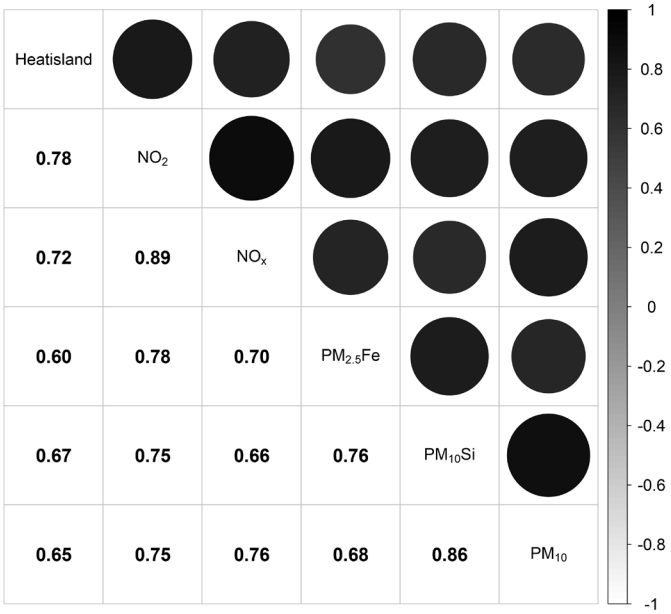
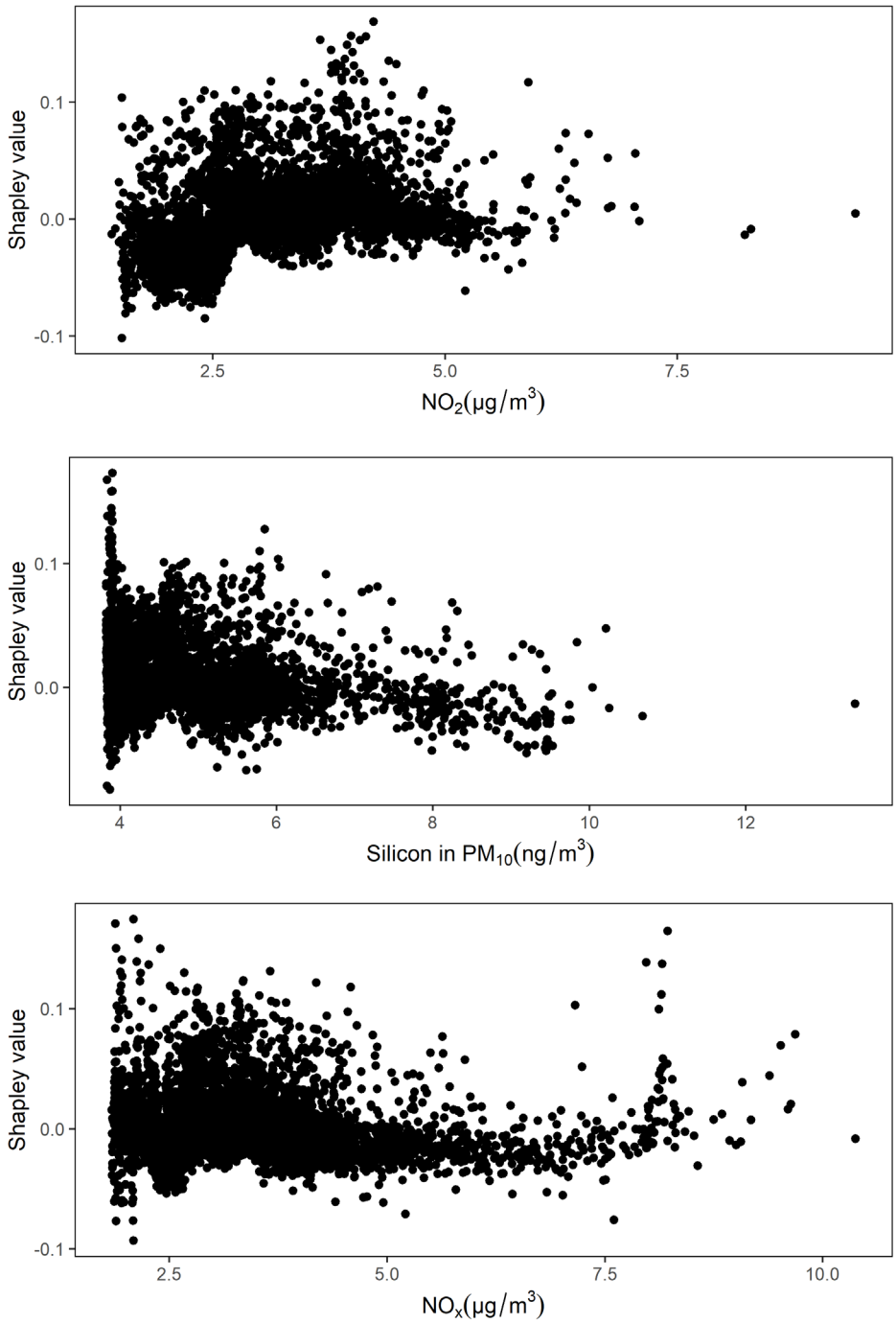
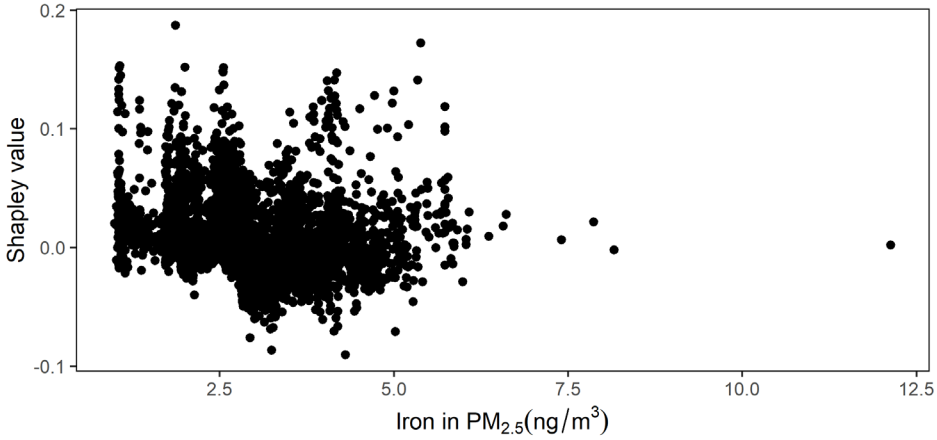
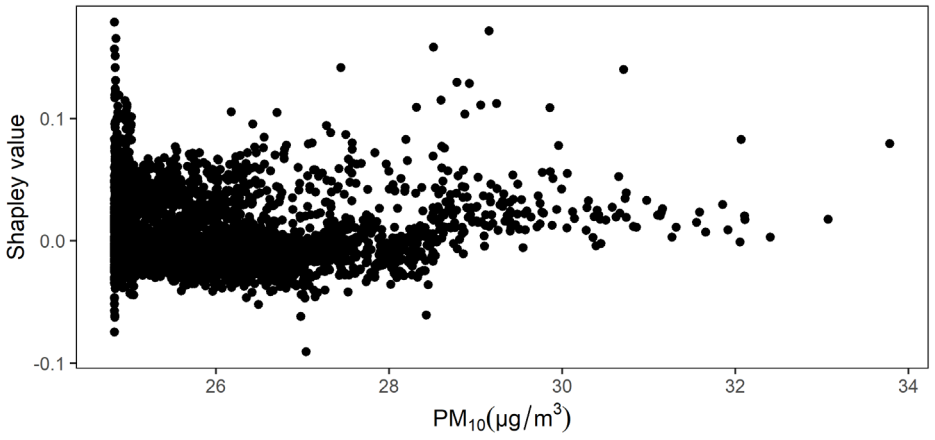
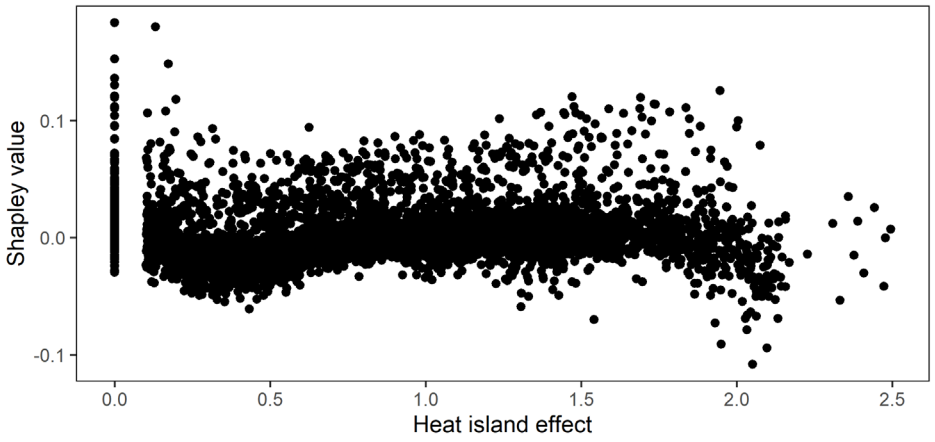


Figure 3. Shapley plot illustrations of the exposures selected by Boruta.




Shapley value
0.2
0.1
0.0
-0.1
2.5
5.0
7.5
10.0
12.5
Iron in $PM_{2.5}(ng/m^3)$


Shapley value
0.1
0.0
-0.1
26
28
30
32
34
$PM_{10}(\mu g/m^3)$


Shapley value
0.1
0.0
-0.1
0.0
0.5
1.0
1.5
2.0
2.5
Heat island effect

SUPPLEMENTARY MATERIAL

Title: A prospective exploration of the urban exposome in relation to headache in the Dutch population-based Occupational and Environmental Health Cohort Study (AMIGO)

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with mutual adjustment for the remaining exposures.

Supplementary Table 1. Data sources for each exposure included in the AMIGO urban exposome and considered in this study.

Exposure	Method	Year	Spatial resolution	Reference(s)
Urban Temperature				
Surface temperature (C◦)	Satellite observations	2016	30x30m	(Remme, 2017)
Urban heat effect (temperature difference to rural surrounding) (C◦)			10x10m	
Road traffic noise				
Combined traffic noise (dB)	Modelled exposure	2016	10x10m^2	(Baliatsas et al., 2016; Martens et al., 2018)
Outdoor light at night				
Light at night (NanoW/cm^2/sr)	Satellite observations	2015	Pixel size ~750x750m	(Elvidge et al., 2017)
Urbanicity and built environment				
Degree of urbanicity (categories from 1 (high) to 5 (low))	Neighbourhood maps	2011	Neighbourhood (PC4)	(Statistiek, 2011)
Distance to major road (km)				
Distance to train station (km)				
Distance to larger train station (km)				
Distance to medical facilities (km)				
Distance to healthier food retailers (km)				
Distance to educational facilities (km)				
Distance to recreational facilities (km)				
Distance to warehouse shops (km)				
Healthy food retailers (frequency)			5km buffer	
Non healthy food retailers (frequency)			1km buffer	
Educational facilities (frequency)			10km buffer	

Warehouse shops (frequency)			20km buffer	
Radiofrequency electromagnetic fields (RF-EMFs)				
Mobile phone call-time (min/day)	Regression calibrated estimates based on self-report	2012		
RF-EMF dose (mJ/Kg/day)	Integrated exposure model (IEM) including the use of mobile phones, cordless phones, laptops and far-field exposure	2012		(van Wel et al., 2021)
Green space density				
100m buffer 1000m buffer	Satellite observations	2016	100m buffer 1000m buffer	(Rhew et al., 2011)
Air pollution				
NO_2 ($\mu g/m^3$) NO_x ($\mu g/m^3$) $PM_{2.5}$ absorbance ($\mu g/m^3$) PM_{10} ($\mu g/m^3$) $PM_{2.5}$ ($\mu g/m^3$) PM coarse ($\mu g/m^3$)		2009	Point-estimate	(Beelen et al., 2013; Eeftens et al., 2012)
UFP particle ($count/cm^3$)		2016	Point-estimate	(Kerckhoffs et al., 2021)
Oxidative Potential (dithiothreitol)		2009	Point-estimate	(Yang et al., 2015)
Oxidative Potential (electron spin resonance) Copper in PM_{10} (ng/m^3) Iron in PM_{10} (ng/m^3) Potassium in PM_{10} (ng/m^3) Nickel in PM_{10} (ng/m^3) Sulfur in PM_{10} (ng/m^3) Silicon in PM_{10} (ng/m^3) Iron in $PM_{2.5}$ (ng/m^3) Potassium in $PM_{2.5}$ (ng/m^3) Sulfur in $PM_{2.5}$ (ng/m^3) Silicon in $PM_{2.5}$ (ng/m^3)	National land use regression models	2009	Point-estimate	(Hoogh et al., 2013)
Quality of drinking water				

Aluminium (µg/l) Natrium (ug/l) Nickel (ug/l) Nitrate (mg/l) Chloride (ug/l) Turbidity (FTE=Formazine Turbidity Units) Fluoride (mg/l) Iron (µg/l) Copper (µg/l) Magnesium (mg/l) Total organic carbon (mg/l) Sulfate (mg/l) Color intensity (Pt/Co-schaal) Electrical conductivity (microS/cm) Aminomethyl phosphonic acid (Pesticide) (µg/l) Arsen (µg/l) Bentazon (herbicide)(µg/l) Bromat (µg/l) Chrome (µg/l) Diprogulic acid (µg/l) Lead (µg/l) Mangan (µg/l) pesticide: Mecoprop (µg/l) Nitrite (µg/l) Trihalomethanes (µg/l) Tritium (Becquerel) Bacteria of the coli group (kve/100 ml) Escherichia coli (kve/100 ml) Smell of drinking water	Drinking water quality map	2012		(*Quality of Drinking Water | RIVM*, n.d.)
Technology use				
Texting-SMS (frequency)	Self-reported	2012		(Reedijk et al., 2018; Slottje et al., 2014)
Browsing on mobile phones (frequency)	Self-reported	2012		
Socio-demographic area-level factors				

Inhabitants in neighbourhood aged 0-14 years (%) Inhabitants in neighbourhood aged 15-24 years (%) Inhabitants in neighbourhood aged 25-44 years (%) Inhabitants in neighbourhood aged 45-64 years (%) Inhabitants in neighbourhood aged 65+ years (%) Single inhabitants in neighbourhood (%) Married inhabitants in neighbourhood (%) Divorced inhabitants in neighbourhood (%) Widowed inhabitants in neighbourhood (%) One-person households (%) Inhabitants with western origins (Europe, North America, Oceania, Indonesia, Japan) (%) Inhabitants with non-western origins (%) Average value of houses (x 1000 euros) Persons with income below 40th percentile (%) Persons with income above 20th percentile (%) Total passenger cars (frequency) Road safety by accident count in 200m buffer (frequency)	Neighbourhood maps	2011	Neighbourhood (PC4)	(Statistiek, 2011)
Perceived exposure				

Perceived exposure to (respectively): air pollution from road traffic, air pollution from other sources, noise from road traffic, noise from other sources, UV radiation from the sun, (RF-) EMFs emitted by mobile phone base stations/Radio/TV antennas, mobile phones, cordless phones, power lines, transformer houses (scale 0 (not at all) – 6 (very much))	Self-reported	2012		(Martens et al., 2017; Reedijk et al., 2018; Slottje et al., 2014)

Supplementary Table 2. Highly correlated exposures and corresponding retained exposure as a proxy for others.

Highly correlated exposures (with Spearman rank correlation coefficient ≥ 0.95)	**Retained exposure as a proxy for others**
Vanadium in $PM_{2.5}$ (ng/m^3) Vanadium in PM_{10} (ng/m^3) Nickel in $PM_{2.5}$ (ng/m^3) Nickel in PM_{10} (ng/m^3)	Nickel in PM_{10} (ng/m^3)
Zinc in PM_{10} (ng/m^3) Zinc in $PM_{2.5}$ (ng/m^3) Potassium in $PM_{2.5}$ (ng/m^3)	Potassium in $PM_{2.5}$ (ng/m^3)
Copper in $PM_{2.5}$ (ng/m^3) Iron in $PM_{2.5}$ (ng/m^3)	Iron in $PM_{2.5}$ (ng/m^3)
Smell of drinking water Taste of drinking water	Smell of drinking water

Supplementary Table 3. Characteristics of the participants who completed the baseline questionnaire (irrespective of their subsequent completion of the follow-up questionnaire) (N=14829).

Sex, n (%)	
Male	6561 (44.2)
Female	8268 (55.8)
Age (years)	
Mean (SD)	50.6 (9.37)
Highest level of education attained, n (%)	
High	4531 (30.6)
Low	10217 (68.9)
Missing	81 (0.5)
Occupation, n (%)	
Employed	10641 (71.8)
Unemployed	4167 (28.2)
Country of origin, n (%)	
The Netherlands	14127 (95.3)
Other	702 (4.7)
BMI group, n (%)	
Normal or underweight	7955 (55.7)
Overweight or obese	6748 (43.5)
Missing	126 (0.8)
Alcohol consumption, n (%)	
No	1936 (13.1)
Yes	12793 (86.3)
Missing	100 (0.6)
Smoking status, n (%)	
No	12484 (84.2)
Yes	2322 (15.7)
Missing	23 (0.1)
Sleep disturbance index	
Mean (SD)	26.8 (19.2)
Missing	230 (1.6%)
General health indicator, n (%)	
Poor	2449 (16.5)
Good	12260 (82.7)
Missing	120 (0.8)
Depression diagnosis, n (%)	
No	12804 (86.3)
Yes	1555 (10.5)
Missing	470 (3.2)
Painkiller use, n (%)	
No	13305 (89.7)
Yes	1022 (6.9)
Missing	502 (3.4)
Weekly headache[a], n (%)	
No	12607 (85.0)
Yes	2069 (14.0)
Missing	153 (1.0)
Severe weekly headache[a], n (%)	
No	13629 (91.9)
Yes	1009 (6.8)
Missing	191 (1.3)

[a]At baseline.

Supplementary Table 4. Description of the exposures considered in this study.

Exposure	Missing (%)	Mean (SD) or n (%)
Urban Temperature		
Surface temperature (C◦)	6.3%	32.5 (2.13)
Urban heat effect (temperature difference to rural surrounding) (C◦)	0.2%	0.848 (0.491)
Road traffic noise		
Combined traffic noise (dB)	-	Lden<55 dB: 5153 (70.2%) Lden>55 dB: 2186 (29.8%)
Outdoor light at night		
Electric light (NanoW/cm^2/sr)	0.2%	12.5 (13.7)
Urbanicity and built environment		
Degree of urbanicity (categories from 1 (high) to 5 (low))	0.3%	1 (high): 618 (8.4%) 2: 1520 (20.7%) 3: 1734 (23.6%) 4: 1770 (24.1%) 5: (low): 1678 (22.9%)
Distance to major road (km)	0.4%	1.57 (0.909)
Distance to train station (km)	0.4%	5.19 (4.62)
Distance to larger train station (km)	0.4%	12.9 (9.21)
Distance to medical facilities (km)	0.4%	1.01 (0.981)
Distance to healthier food retailers (km)	0.4%	0.768 (0.671)
Distance to educational facilities (km)	0.4%	0.596 (0.438)
Distance to recreational facilities (km)	0.4%	2.30 (1.99)
Distance to warehouse shops (km)	0.4%	3.27 (2.66)
Healthy food retailers	0.4%	71.8 (107)
Non healthy food retailers (frequency)	0.4%	13.1 (31.2)
Educational facilities (frequency)	0.9%	79.5 (81.5)
Warehouse shops (frequency)	0.4%	17.0 (11.4)
Radiofrequency electromagnetic fields (RF-EMFs)		
Mobile phone call-time (min/day)	0.7%	23.5 (22.9)

RF-EMF dose (mJ/Kg/day)	0.3%	254 (251)
Green space density		
100m buffer	0.2%	0.488 (0.133)
1000m buffer	0.2%	0.535 (0.113)
Air pollution		
NO_2 (μg/m^3)	1.5%	22.2 (5.59)
NO_x (μg/m^3)	1.5%	31.9 (9.75)
$PM_{2.5}$ absorbance (μg/m^3)	1.5%	1.21 (0.196)
PM_{10} (μg/m^3)	1.5%	24.5 (0.931)
$PM_{2.5}$ (μg/m^3)	1.5%	16.5 (0.664)
PM coarse (μg/m^3)	1.5%	8.18 (0.651)
UFP particle (count/cm^3)	-	9460 (2040)
Oxidative Potential (dithiothreitol)	1.5%	1.16 (0.193)
Oxidative Potential (electron spin resonance)	1.5%	889 (147)
Copper in PM_{10} (ng/m^3)	-	12.1 (3.26)
Iron in PM_{10} (ng/m^3)	-	350 (99.8)
Potassium in PM_{10} (ng/m^3)	-	202 (14.3)
Nickel in PM_{10} (ng/m^3)	-	2.03 (0.798)
Sulfur in PM_{10} (ng/m^3)	-	1010 (41.1)
Silicon in PM_{10} (ng/m^3)	-	345 (67.4)
Iron in $PM_{2.5}$ (ng/m^3)	-	76.0 (21.5)
Potassium in $PM_{2.5}$ (ng/m^3)	-	116 (9.48)
Sulfur in $PM_{2.5}$ (ng/m^3)	0.1%	883 (52.0)
Silicon in $PM_{2.5}$ (ng/m^3)	-	79.6 (12.1)
Quality of drinking water		
Aluminium (μg/l)	0.2%	1.62 (3.02)
Natrium (ug/l)	0.2%	35.3 (26.2)
Nickel (ug/l)	0.2%	0.743 (1.35)
Nitrate (mg/l)	0.2%	4.93 (5.32)
Chloride (ug/l)	0.2%	41.2 (31.0)
Turbidity (FTE=Formazine Turbidity Units)	0.2%	0.10 (0.20)
Fluoride (mg/l)	0.2%	0.0785 (0.0589)
Iron (μg/l)	0.2%	10.1 (18.6)
Copper (μg/l)	0.2%	2.40 (6.41)
Magnesium (mg/l)	0.2%	7.55 (2.63)
Total organic carbon (mg/l)	0.2%	1.70 (1.60)
Sulfate (mg/l)	0.2%	32.9 (26.4)
Color intensity (Pt/Co-schaal)	0.2%	3.04 (4.01)
Electrical conductivity (microS/cm)	0.2%	43.4 (11.8)
Aminomethyl phosphonic acid (Pesticide) (μg/l)	0.2%	0 (μg/l): 7074 (96.4%) >0 (μg/l): 251 (3.4%)

Arsen (µg/l)	0.2%	0 (µg/l): 6303 (85.9%) >0 (µg/l): 1022 (13.9%)
Bentazon (herbicide)(µg/l)	0.2%	0 (µg/l): 6528 (88.9%) >0 (µg/l): 797 (10.9%)
Bromat (µg/l)	0.2%	0 (µg/l): 6355 (86.6%) >0 (µg/l): 970 (13.2%)
Chrome (µg/l)	0.2%	0 (µg/l): 6888 (93.9%) >0 (µg/l): 437 (6.0%)
Diprogulic acid (µg/l)	0.2%	0 (µg/l): 6417 (87.4%) >0 (µg/l): 908 (12.4%)
Lead (µg/l)	0.2%	0 (µg/l): 7197 (98.1%) >0 (µg/l): 128 (1.7%)
Mangan (µg/l)	0.2%	0 (µg/l): 7189 (98.0%) >0 (µg/l): 136 (1.9%)
pesticide: Mecoprop (µg/l)	0.2%	0 (µg/l): 7195 (98.0%) >0 (µg/l): 130 (1.8%)
Nitrite (µg/l)	0.2%	35.3 (26.2)
Trihalomethanes (µg/l)	0.2%	0 (µg/l): 6409 (87.3%) >0 (µg/l): 916 (12.5%)
Tritium (Becquerel)	0.2%	0 (µg/l): 7155 (97.5%) >0 (µg/l): 170 (2.3%)
Bacteria of the coli group (kve/100 ml)	0.2%	0 (µg/l): 6997 (95.3%) >0 (µg/l): 328 (4.5%)
Escherichia coli (kve/100 ml)	0.2%	0 (µg/l): 7204 (98.2%) >0 (µg/l): 121 (1.6%)
Smell of drinking water	0.2%	0 (µg/l): 7066 (96.3%) >0 (µg/l): 259 (3.5%)
Technology use		
Texting-SMS (frequency)	0.9%	0 (low): 5903 (80.4%) 1 (medium): 1237 (16.9%) 2 (high): 133 (1.8%)
Browsing on mobile phones (frequency)	1.0%	0 (low): 5342 (72.8%) 1 (medium): 783 (10.7%) 2 (high): 1144 (15.6%)
Socio-demographic area-level factors		
Inhabitants in neighbourhood aged 0-14 years (%)	0.3%	18.0 (4.97)
Inhabitants in neighbourhood aged 15-24 years (%)	0.3%	11.9 (3.64)
Inhabitants in neighbourhood aged 25-44 years (%)	0.3%	25.3 (6.23)
Inhabitants in neighbourhood aged 45-64 years (%)	0.3%	29.4 (5.46)

Inhabitants in neighbourhood aged 65+ years (%)	0.3%	15.4 (7.11)
Single inhabitants in neighbourhood (%)	0.3%	45.3 (7.91)
Married inhabitants in neighbourhood (%)	0.3%	43.6 (7.68)
Divorced inhabitants in neighbourhood (%)	0.3%	6.07 (2.34)
Widowed inhabitants in neighbourhood (%)	0.3%	5.11 (2.91)
One-person households (%)	0.3%	30.4 (12.1)
Inhabitants with western origins (Europe, North America, Oceania, Indonesia, Japan) (%)	0.3%	8.00 (3.86)
Inhabitants with non-western origins (%)	9.7%	11.2 (12.2)
Average value of houses (x 1000 euros)	1.6%	251 (71.4)
Persons with income below 40th percentile (%)	1.1%	39.1 (6.92)
Persons with income above 20th percentile (%)	1.1%	20.4 (7.76)
Total passenger cars (frequency)	0.2%	1590 (1400)
Road safety by accident count in 200m buffer (frequency)	0.02%	1.23 (3.91)
Perceived exposure		
Air pollution from road traffic	3.3%	0 (not at all): 1367 (18.6%) 1: 2533 (34.5%) 2: 1299 (17.7%) 3: 1027 (14.0%) 4: 648 (8.8%) 5: 302 (4.1%) 6 (very much): 163 (2.2%)
Air pollution from other sources	3.4%	0 (not at all): 3033 (41.3%) 1: 2193 (29.9%) 2: 904 (12.3%) 3: 559 (7.6%) 4: 307 (4.2%) 5: 200 (2.7%) 6 (very much): 143 (1.9%)
		0 (not at all): 1520 (20.7%) 1: 2862 (39.0%)

		2: 1287 (17.5%)
Noise from road traffic	3.4%	3: 791 (10.8%)
		4: 485 (6.6%)
		5: 276 (3.8%)
		6 (very much): 118 (1.6%)
		0 (not at all): 2755 (37.5%)
		1: 2463 (33.6%)
		2: 938 (12.8%)
Noise from other sources	3.4%	3: 545 (7.4%)
		4: 324 (4.4%)
		5: 203 (2.8%)
		6 (very much): 111 (1.5%)
		0 (not at all): 864 (11.8%)
		1: 2429 (33.1%)
		2: 2031 (27.7%)
UV radiation from the sun	3.5%	3: 1447 (19.7%)
		4: 420 (5.7%)
		5: 117 (1.6%)
		6 (very much): 31 (0.4%)
(RF-)EMFs emitted by:		
		1: 2332 (31.8%)
mobile phone base		2: 928 (12.6%)
stations/Radio/TV	3.5%	3: 563 (7.7%)
antennas		4: 189 (2.6%)
		5: 81 (1.1%)
		6 (very much): 49 (0.7%)
		0 (not at all): 1313 (17.9%)
		1: 2929 (39.9%)
		2: 1328 (18.1%)
mobile phones	3.6%	3: 983 (13.4%)
		4: 399 (5.4%)
		5: 251 (3.4%)
		6 (very much): 136 (1.9%)
		0 (not at all): 1284 (17.5%)
		1: 2873 (39.1%)
		2: 1427 (19.4%)
cordless phones	3.7%	3: 1050 (14.3%)
		4: 398 (5.4%)
		5: 206 (2.8%)
		6 (very much): 101 (1.4%)
		0 (not at all): 4938 (67.3%)
		1: 1545 (21.1%)
		2: 484 (6.6%)
power lines	3.6%	3: 250 (3.4%)
		4: 63 (0.9%)
		5: 34 (0.5%)
		6 (very much): 25 (0.3%)
		0 (not at all): 4955 (67.5%)

transformer houses	3.4%	1: 1608 (21.9%) 2: 465 (6.3%) 3: 231 (3.1%) 4: 43 (0.6%) 5: 19 (0.3%) 6 (very much): 18 (0.2%)

Supplementary Table 5. Average treatment effects (ATEs) and related standard errors (SEs) estimated with causal forests for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline. Causal forests including Copper in $PM_{2.5}$ as a proxy for Iron in $PM_{2.5}$.

Exposure	ATE[a] (SE)
NO_2 (μg/m^3)	0.007 (0.004)
PM_{10} (μg/m^3)	0.006 (0.004)
Heat island effect (C◦)	0.006 (0.007)
NO_x (μg/m^3)	0.004 (0.004)
Copper in $PM_{2.5}$ (ng/m^3)	0.002 (0.004)
Silicon in PM_{10} (ng/m^3)	0.003 (0.004)

[a]Results for air pollutants indicate changes per interquartile range (IQR) increase in mean air pollution exposure.

Supplementary Table 6. Comparison of "high" and "low" out-of-bag CATE regions: causal forests estimated on each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline.

Exposure	"High" region CATE (SE)	"Low" region CATE (SE)	Difference in CATEs (95% CI)
NO_2 ($\mu g/m^3$)	0.013 (0.007)	0.003 (0.005)	0.010 (-0.007 – 0.027)
PM_{10} ($\mu g/m^3$)	0.003 (0.005)	0.007 (0.005)	-0.004 (-0.018 – 0.010)
Heat island effect (C◦)	0.007 (0.011)	0.006 (0.008)	0.001 (-0.025 – 0.027)
NO_x ($\mu g/m^3$)	0.006 (0.005)	0.001 (0.004)	0.005 (-0.008 – 0.018)
Iron in $PM_{2.5}$ (ng/m^3)	-0.003 (0.007)	0.007 (0.005)	-0.010 (-0.026 – 0.006)
Silicon in PM_{10} (ng/m^3)	0.003 (0.006)	0.002 (0.005)	0.001 (-0.015 – 0.017)

Supplementary Table 7. Average treatment effects (ATEs) and related standard errors (SEs) estimated with causal forests for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline, with mutual adjustment for the remaining exposures.

Exposure	ATE[a] (SE)
NO_2 (μg/m^3)	0.058 (0.022)
PM_{10} (μg/m^3)	0.002 (0.014)
Heat island effect (C◦)	-0.019 (0.017)
NO_x (μg/m^3)	0.011 (0.018)
Iron in $PM_{2.5}$ (ng/m^3)	-0.016 (0.010)
Silicon in PM_{10} (ng/m^3)	-0.045 (0.051)

[a]Results for air pollutants indicate changes per interquartile range (IQR) increase in mean air pollution exposure.

Supplementary Table 8. Comparison of "high" and "low" out-of-bag CATE regions: causal forests estimated on each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline, with mutual adjustment for the remaining exposures.

Exposure	"High" region CATE (SE)	"Low" region CATE (SE)	Difference in CATEs (95% CI)
NO_2 (μg/m^3)	0.083 (0.031)	0.001 (0.015)	0.082 (0.015 – 0.149)
PM_{10} (μg/m^3)	0.017 (0.012)	0.014 (0.017)	0.002 (-0.039 – 0.043)
Heat island effect (C◦)	0.000 (0.022)	-0.038 (0.026)	0.038 (-0.029 – 0.105)
NO_x (μg/m^3)	-0.008 (0.012)	-0.015 (0.015)	0.007 (-0.031 – 0.038)
Iron in $PM_{2.5}$ (ng/m^3)	-0.012 (0.012)	0.003 (0.012)	-0.015 (-0.049 – 0.034)
Silicon in PM_{10} (ng/m^3)	-0.041 (0.086)	-0.050 (0.055)	0.009 (-0.191 – 0.209)

Supplementary Table 9. Average treatment effects (ATEs) and related standard errors (SEs) estimated with causal forests for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline.

Exposure	ATE[a] (SE)
NO_2 (μg/m^3)	0.007 (0.004)
PM_{10} (μg/m^3)	0.006 (0.004)
Heat island effect (C◦)	0.006 (0.007)
NO_x (μg/m^3)	0.004 (0.004)
Iron in $PM_{2.5}$ (ng/m^3)	0.003 (0.004)
Silicon in PM_{10} (ng/m^3)	0.003 (0.004)
PM_{coarse} (μg/m^3)	0.005 (0.004)
Potassium in PM_{10} (ng/m^3)	0.002 (0.004)
Road traffic noise (dB)	0.008 (0.007)

[a]Results for air pollutants indicate changes per interquartile range (IQR) increase in mean air pollution exposure.

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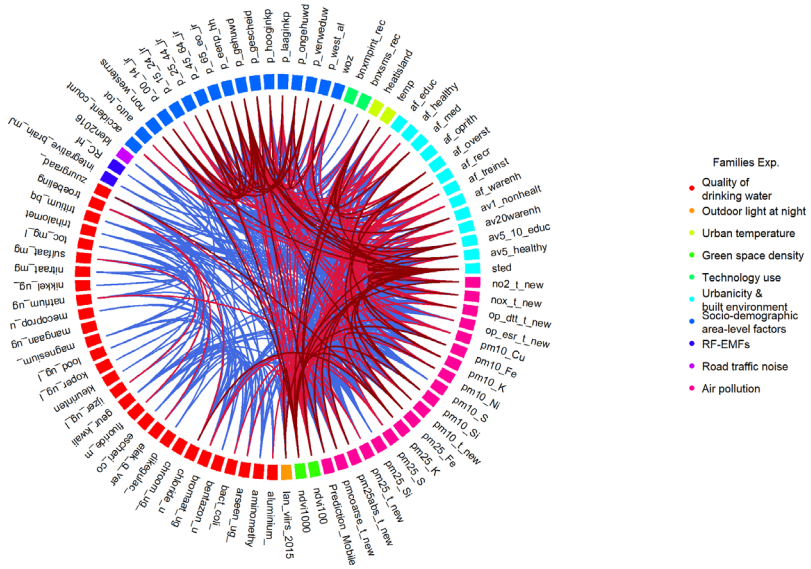
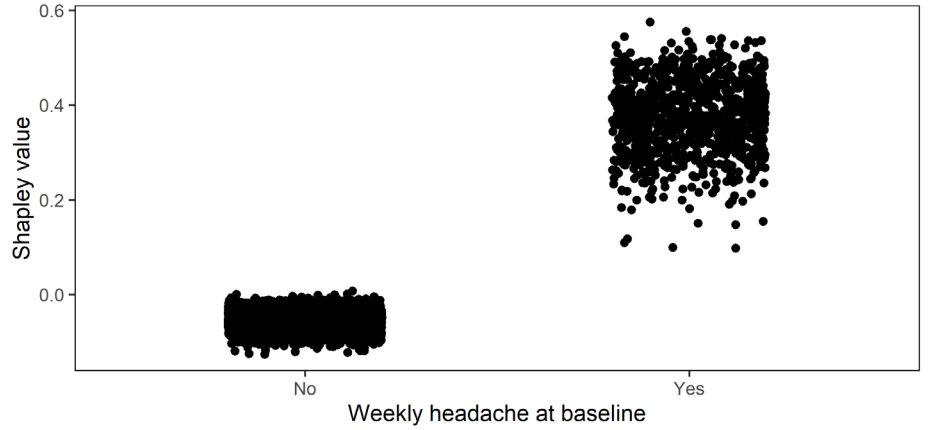
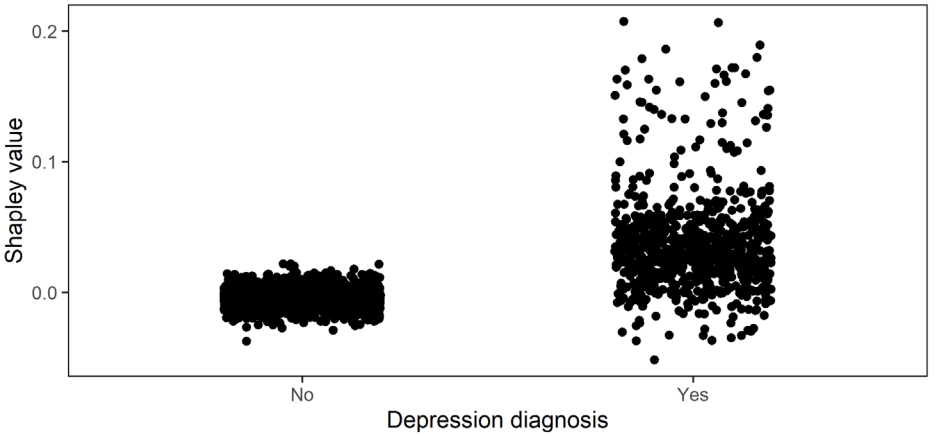
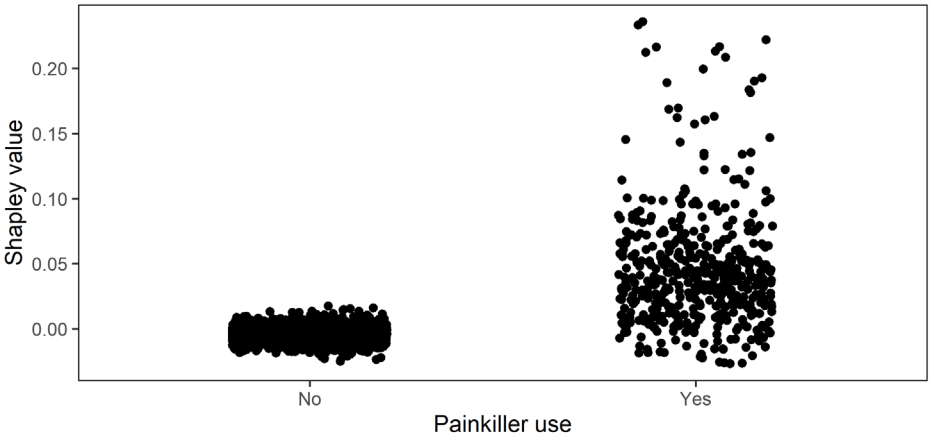
Supplementary Figure 1. The circos of correlation plot showing inter-family correlations between exposures and their domains at baseline.

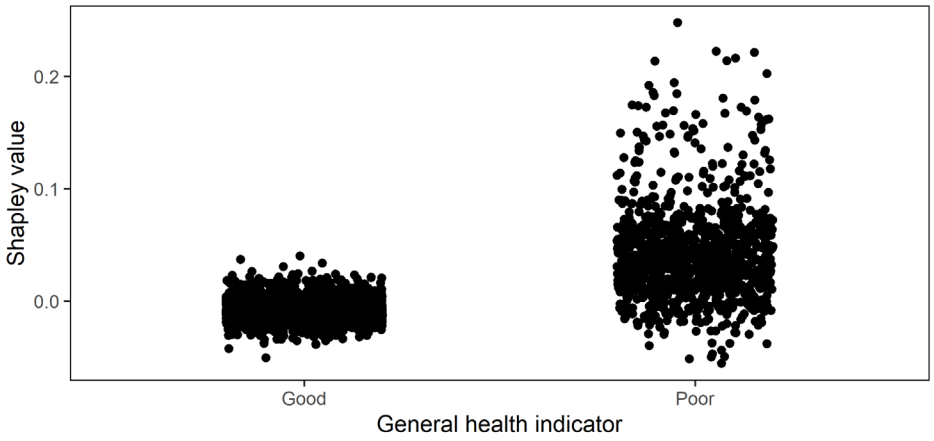


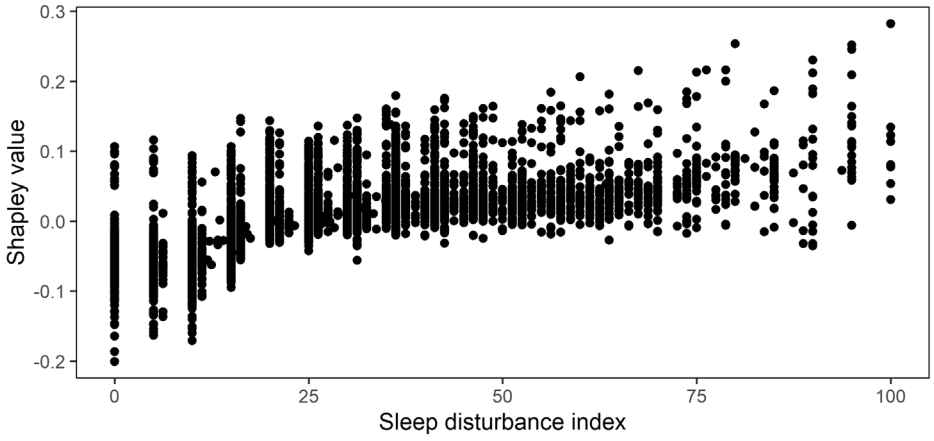
Supplementary Figure 2. Shapley plot illustrations of the covariates selected by Boruta.

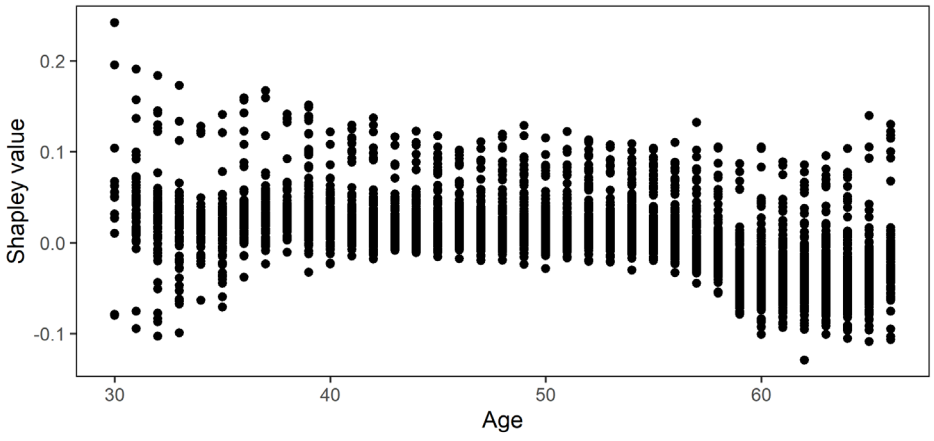




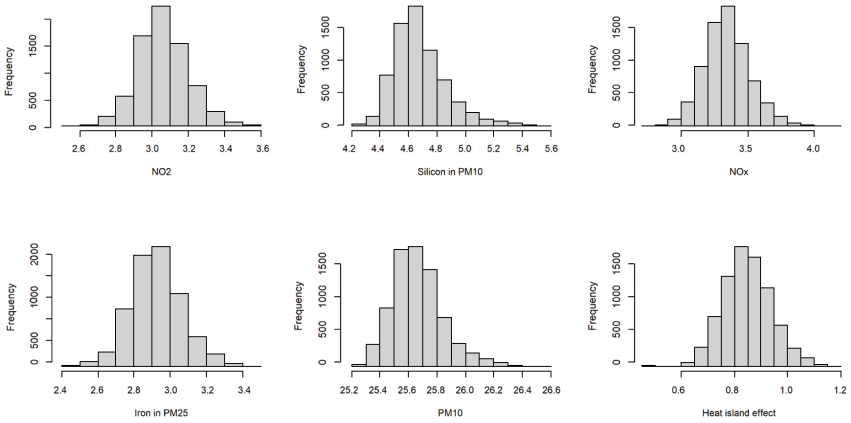



Shapley value
0.2
0.1
0.0
Good
Poor
General health indicator

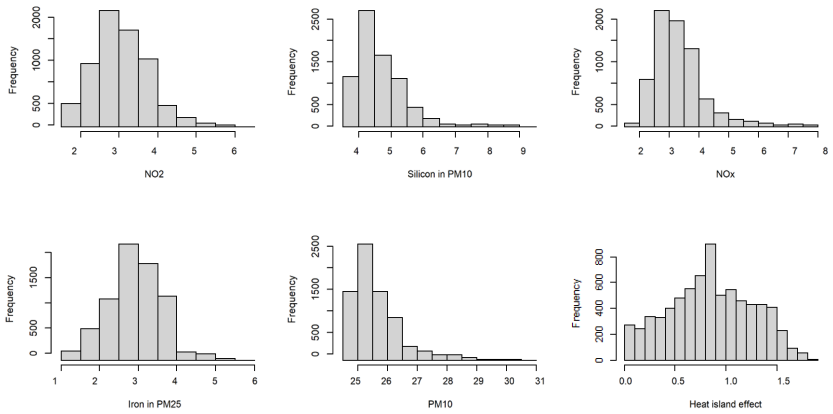

Shapley value
0.3
0.2
0.1
0.0
-0.1
-0.2
0
25
50
75
100
Sleep disturbance index


Shapley value
0.2
0.1
0.0
-0.1
30
40
50
60
Age

Supplementary Figure 3. Distribution of exposure propensity weights with causal forests trained for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline.



Supplementary Figure 4. Distribution of exposure propensity weights with causal forests trained for each exposure separately, adjusted for age, depression diagnosis, painkiller use, general health indicator, sleep disturbance index and weekly headache at baseline, with mutual adjustment for the remaining exposures.



A prospective exploration of the urban exposome in relation to headache in the Dutch population-based Occupational and Environmental Health Cohort Study (AMIGO)

Painkiller use in the AMIGO questionnaire.

1. Have you used the following (prescribed) medications in the past 12 months? (response categories: yes, no)
    - painkiller(s)

   (if painkiller(s) was selected => answer next questions).

2. How often in the past 12 months have you taken the following painkillers? (response categories: at least 1/day, at least 1/week, at least 1/month, rarely, never).

    a. Paracetamol (e.g. Paracetamol, Chefarine, Citrosan, Finimal, Panadol Plus, Femerital, Saridon).
    b. Ibuprofen (e.g. Advil, Brufen, Nurofen, Sarixell, Spidifen).
    c. Acetylsalicylic acid (e.g. Aspirin, Aspro, Aspegic, Alka-Seltzer).
    d. Other painkillers (e.g. Codeine).

Chapter 6: General Discussion

The main objective of this thesis was to propose informative approaches for the analysis of environmental factors commonly encountered in everyday life in relation to health outcomes, using data from prospective studies across different scenarios. These approaches aimed to provide valuable insights and understanding of exposure-outcome relationships, including potential mechanisms of action and underlying causal pathways, to prevent health effects. This was accomplished through careful evaluation of pre-analytical aspects of the study concerning design and hypotheses, optimisation of available data, identification of the most appropriate analytical methods, and critical interpretation of the results. For this purpose, data from large prospective epidemiological studies were analysed using a combination of statistical and machine learning techniques, which include multi-state Markov models, weighted quantile sum regression and boosted regression tree models, Boruta and causal forests, and extensions of regression techniques within the causal inference framework such as the generalised propensity score for single exposures and its multivariate version.
In Chapter 6, I first present the main findings of this thesis's studies. Following this summary, I navigate through the approaches proposed to identify underlying mechanisms of action and address the most relevant challenges encountered across the studies, highlighting the advantages and limitations of the different methods, and providing policy implications and possible directions for future research.

Main findings

In Chapter 2, we explored two potential exposure-outcome pathways concerning mobile phone use and headaches, using pooled data from the Dutch and UK cohorts of COSMOS (N=78,437). Results from multivariable logistic regression models showed that baseline mobile phone use for calling and texting was associated with headaches at follow-up. Interestingly, in the mutually adjusted model for both call-time and texting, we observed considerably attenuated risk estimates for call-time. In contrast, associations with texting were still strong and robust to adjustment, with a clear exposure-outcome relationship. These results suggested that, due to the negligible exposure to RF-EMFs from texting, mechanisms other than RF-EMFs were responsible for the increased risk of headache that we found among mobile phone users. These mechanisms likely reflected lifestyle, other exposures, or behavioural factors associated with mobile phone use.

In Chapter 3, we explored the temporal dynamics of attribution of health complaints to RF-EMFs (IEI-RF) in the subcohort of AMIGO (N=892). Specifically, we assessed factors related to developing, maintaining, or discarding IEI-RF over the course of 10 years by modelling the process in which participants move through a series of states of IEI-RF

with multi-state Markov models. Furthermore, we applied logistic regression to prospectively explore predictors of electromagnetic hypersensitivity without the condition of attributing health complaints to RF-EMF exposure (EHS). Results showed that prevalence of IEI-RF was generally low and remained stable over time. Interestingly, over 10 years of follow-up, we observed a high probability of no longer attributing symptoms to RF-EMF exposure, which suggested that IEI-RF may be a more transient condition than previously assumed. Finally, RF-EMF perceptions, non-specific symptom reporting, and sleep disturbances at baseline were predictive of the notion of being EHS at 10 years follow-up, regardless of whether reporting health complaints attributed to RF-EMF exposure.

In Chapter 4, we adopted a pluralistic approach to prospectively explore the relationship between a mixture of air pollutants and overall mortality in LIFEWORK (N=86,882). Through the use of methods designed for the analysis of high-dimensional exposure data, namely weighted quantile sum (WQS) regression and boosted regression trees (BRT), we identified the most relevant components within the mixture in relation to the outcome, accounting for the strong correlations, interactions and nonlinearities. Based on these results, we estimated a multivariate generalised propensity score model to jointly estimate the causal effects of the pollutants on overall mortality. Results showed that, by using novel methods for causal inference and mixture modelling in a large prospective cohort, we could strengthen the causal interpretation of air pollution effects on mortality, identifying the most relevant contributors and emphasising the primary role of $PM_{2.5}$ within the pollutant mixture.

In Chapter 5, we prospectively explored the urban exposome of AMIGO (N=7,339) in relation to headaches by using a combination of machine learning techniques designed to reduce complexities in high-dimensional settings and estimate causal effects. Specifically, we first applied Boruta to identify relevant exposures in the exposome-outcome association, and then estimated causal forest to quantify the effect of these exposures on the occurrence of headache. Boruta selected five air pollutants (NO_2, NO_X, PM_{10}, silicon in PM_{10}, iron in $PM_{2.5}$) and one urban temperature measure (heat island effect) as factors contributing to the reporting of weekly headache at follow-up. The estimated causal effect of each exposure on weekly headache indicated positive associations for all exposures, with NO_2 displaying the largest effect. Of note, accounting for confounding by co-exposure resulted in less precise effect estimates. In conclusion, these results highlighted the relevance of air pollution exposure and heat island effects in reporting weekly headaches in AMIGO.

Unraveling the mechanisms of action of environmental exposures on health necessitates a comprehensive approach

Despite the ubiquitous nature of air pollution and RF-EMFs in the environment, they have very distinct features that require different approaches to understand their mode of action.

While the mechanisms underlying the health effects of air pollution are relatively well-understood, and they involve inflammation, oxidative stress, and systemic responses triggered by exposure to particulate matter and gaseous pollutants (Block & Calderón-Garcidueñas, 2009; Brunekreef & Holgate, 2002; Leikauf et al., 2020; Miller, 2020), those concerning RF-EMF exposure, particularly at the low levels of exposure normally encountered in the population, remain more uncertain. The accepted mechanism of action of RF-EMF exposure to date includes a thermal effect from absorbed energy (D'Andrea et al., 2007). Furthermore, oxidative stress is proposed as a potential biological response to RF-EMFs in a number of experimental studies, such as those investigating the effects on nervous and reproductive systems (Henschenmacher et al., 2022; Kamali et al., 2018; Tkalec et al., 2007; Yüksel et al., 2016), although it remains unclear whether oxidative stress may result in harmful health effects at the generally low exposure levels that are experienced by the general population. On the other hand, epidemiological studies exploring the health effects associated with long-term RF-EMF exposure from the use of mobile phones struggle to provide definitive evidence about potential mechanisms involved (Boileau et al., 2020; Feychting et al., 2024; INTERPHONE Study Group, 2010; Schüz et al., 2006; Swerdlow et al., 2011; Tettamanti et al., 2020).

In studies investigating health outcomes such as headache and migraine, the identification of mechanisms of action becomes even more challenging due to the transient nature of the symptoms (Auvinen et al., 2019; Frei et al., 2012; Martens et al., 2018; Schüz et al., 2009; Szyjkowska et al., 2014; Wang et al., 2017). Results from these studies can be difficult to interpret as no clear distinction is traditionally made, within each study, between aspects of electronic device use directly related to RF-EMF exposure and other features associated with negligible RF-EMF exposure, which still represent potential risk factors for headache symptoms in the population. In this regard, growing evidence is supporting the hypothesis of a link between headaches and certain aspects of electronic device use, such as screen time or texting (Langdon et al., 2024; Lund et al., 2022; Montagni et al., 2016; Tsantili et al., 2022). Therefore, to elucidate potential mechanisms of action, it would be advantageous to explore exposure constructs that aid in disentangling the relationship between exposure and outcome.

Following these considerations, two potential adverse exposure-outcome pathways in the association between mobile phone use and headaches can be identified (Chapter 2). The first route relates to RF-EMF exposure, with the duration of voice calling on a mobile phone considered as a proxy for the exposure to the head of the participants.

This is a common approach used to quantify RF-EMF exposure in epidemiological studies exploring the health effects from long-term use of mobile phones (Auvinen et al., 2019; Schüz et al., 2009), given that the actual measurement of RF-EMFs in large populations proves impractical due to time and costs that such implementation would require. In this regard, efforts are underway to develop mobile phone applications able to accurately measure personal absorbed RF-EMF doses to map participants' exposure in large epidemiological studies (*Exposure To electromAgnetic fIelds and plaNetary Health | ETAIN Project | Fact Sheet | HORIZON*, 2022).

The second route pertains to distinct aspects of mobile phone use with negligible RF-EMF exposure, such as sending text messages. In Chapter 2, results from the single-exposure models including voice calling and texting as exposures of interest, respectively, showed an increase in the risk of reporting headache with increasing call-time and frequency of text messages, with clear exposure-outcome relationships. The two-exposure model with mutual adjustment for both call-time and texting produced considerably attenuated risk estimates for call-time, while associations with texting were still strong and robust to adjustment, with a clear increase in reporting headache with increasing texting, which was no longer observed for call-time.
This approach demonstrates that, by using distinct exposure metrics as proxy for RF-EMF exposure and other usage with negligible RF-EMF exposure, it was possible to shed light on pertinent questions regarding the underlying mechanisms of action of mobile phone use in relation to headache reporting, and disentangle the exposure-outcome association by excluding the RF-EMF route. In particular, our findings point towards the fact that RF-EMF exposure has no effect on the reporting of headaches and suggest that factors other than RF-EMFs may be involved (Chapter 2).
Regarding the exact mechanisms at play, be it texting, screen time, or other factors related to the usage, it is difficult to draw definitive conclusions. In this scenario, unmeasured factors, such as lifestyle, other exposures, or behavioural aspects related to mobile phone use that were not directly evaluated in the study could potentially mediate the effect of texting that was observed on the occurrence of headache. Therefore, to determine the exact mechanisms triggering headache among mobile phone users, further analyses (e.g. mediation analysis) should be conducted to quantify the impact of these factors along with texting on reporting symptoms.

For exposures such as RF-EMFs, a major challenge in the identification of potential mechanisms of action is represented by the exposure itself, which naturally undergoes frequent changes over time. This scenario becomes even more challenging when the study outcome is also highly transient. In this specific context, the underlying causes of action must be explored while addressing the temporal variability of both exposure and

outcome.

As case study, we explored the temporal dynamics of attribution of health complaints to RF-EMF exposure (IEI-RF) using longitudinal data from the subcohort of AMIGO (Chapter 3).

There are several challenges that researchers encounter when studying IEI-RF, which are introduced in Chapter 1. Among those, the uncertainty in the underlying mechanisms of action of IEI-RF is one of the most prominent. Previous studies, in fact, were not able to ascertain these mechanisms, and current evidence is limited regarding the potential pathways, although psychosocial factors were identified as potential triggers for the condition (Baliatsas et al., 2009; Dieudonné, 2016; Martens et al., 2018; Stein & Udasin, 2020).

Multi-state Markov models represent a flexible tool for exploring and determining the most plausible pathway among those identified in previous studies (Dieudonné, 2016, 2020; Martens et al., 2017). A multi-state Markov model is a continuous time stochastic process suitable to model the process in which participants move through a series of states of IEI-RF, defined as presence or absence of symptoms attributed to RF-EMFs. Multi-state Markov models are traditionally employed in studies estimating rates of transition between stages of disease progression, including the average duration spent in a particular state ("sojourn time"), and rely on the assumption that future evolution only depends on the current state (Kalbfleisch & Lawless, 1985). Besides applications in healthcare and epidemiology, multi-state Markov models are frequently applied across various domains, including economics, finance, and social sciences (Chamboko & Bravo, 2020; Hougaard, 1999).

In Chapter 3, we followed this approach to evaluate the dynamics of IEI-RF at three time points over the course of 10 years. Here, multi-state Markov models were estimated with IEI-RF included as dependent variable, and perception of RF-EMF exposure and risk, self-reported non-specific symptoms, and sleep disturbances as time-dependent covariates. Incorporating covariate data assessed at the same time points as the dependent variable is essential for capturing potential time-variant effects and understanding these factors' role on transition rates of IEI-RF. By using this approach, we accounted for several factors in estimating the instantaneous risk of transitioning from one state into another of IEI-RF that, in previous studies, were identified as potential risk factors for IEI-RF.

Results suggested that individuals in AMIGO were likely to attribute symptoms to RF-EMF exposure, possibly to help explain a health issue they may be experiencing, for which no diagnosis was made, and therefore alleviate the uncertainty regarding the underlying cause.

This conclusion was driven by important considerations regarding the remaining two potential pathways, which followed directly the interpretation of results of the multi-

state Markov models: first, the biological pathway indicates RF-EMF exposure causes symptoms. Without direct exposure measurements over time, exploring this pathway is limited. Previous research shows personal exposure is mainly influenced by device use, especially phone calls (van Wel et al., 2021). Reduction in exposure should align with behaviour changes, yet those no longer attributing symptoms to RF-EMF exposure tended to report higher exposure perception later on, which is unexpected. Second, the cognitive pathway suggests that perceived exposure and risk trigger a nocebo response leading to symptoms. In Chapter 3, we showed that higher perceived risk and exposure were associated with symptom attribution, indicating the relevance of nocebo effects. However, participants reporting symptoms at earlier time points but not later ones tended to increase exposure and risk perception, contradicting the cognitive hypothesis. This suggests symptoms induced by nocebo effects may not persist in our study population.

The following considerations contributed to gaining valuable insights into the time course of symptoms attributed to RF-EMFs and identifying the most plausible mechanism of action: first, the specific study design, which involved collecting data on perceived exposure and risk, as well as the attribution of health complaints to RF-EMF exposure over a span of more than two time points throughout a period of 10 years, was a key factor to address temporal variation of IEI-RF.
Second, a clear distinction has to be made between IEI-RF and EHS. This is not always the case in previous studies, where IEI-RF and EHS are often defined using heterogeneous criteria which may further increase uncertainty in identifying the underlying mechanisms (Baliatsas et al., 2012). An accurate definition of IEI-RF and EHS is essential to effectively capture participants who attributed symptoms to the exposure. This group of participants would benefit the most from interventions aimed at alleviating their symptoms, therefore their identification is crucial.
Third, by applying multi-state Markov models, we estimated the chance of transitioning between the two states of IEI-RF. This revealed the transient nature of this condition and identified important contributors influencing the dynamics, ultimately leading to the exclusion of the implausible pathways among those previously hypothesised.

In conclusion, the approach outlined in Chapter 3 represents a valid strategy to explore underlying mechanisms of action in scenarios where both exposures and outcomes are difficult to assess and subject to fluctuations over time. While our study possibly represents the most extensive exploration of IEI-RF dynamics over a long time period including a relatively large study population, it is important to note that the low prevalence of IEI-RF in the subcohort of AMIGO hindered our ability to estimate multi-state Markov models with mutual adjustment for potential confounders in the exposure-outcome association.

This approach is therefore recommended in scenarios where longitudinal data on exposures and outcomes is available across multiple time points for a relatively large study populations. Furthermore, to avoid sparse data bias, the outcome should not represent a rare condition in the population. This is necessary to successfully estimate multi-state Markov models while accounting for potential confounding in the exposure-outcome association over time.

Of note, in situations where the states of the Markov process are "hidden" and therefore not directly observed, a possible approach is provided by Hidden Markov models (HMMs). A HMM is a statistical model used to describe the evolution of observable events that depend on underlying states, which are not directly observable. In particular, a HMM consists of a two-dimensional stochastic process where the observed data are determined by a probability distribution conditionally on the latent states (Jackson, 2011). While these models (and their extensions) have historically found their place in computational biology and bioinformatics (McClintock et al., 2020; Yoon, 2009) as well as speech and signal processing (Juang & Rabiner, 1991), they also find potential for applications in (environmental) epidemiology, typically to model the progression of chronic diseases (Chadeau-Hyam et al., 2014; Powell et al., 2019).

For certain exposures, such as air pollution, the mechanisms of action are relatively well-understood. However, by identifying the main contributors within a mixture of air pollutants in relation to an outcome, it is possible to further explore underlying pathways. In this context, the most urgent research questions for policy action pertain to the overall mixture effect and the identification of the components within the mixture showing the largest impact on the outcome while taking into account the co-occurrence of the exposures.
A possible approach to tackle these questions is presented in the study exploring the relationship between a mixture of air pollutants and overall mortality which, by emphasising the primary role of $PM_{2.5}$ within the pollutant mixture, provides valuable insights into the underlying mechanisms of action (Chapter 4).

At a more general level, an initial step in the identification of potential mechanisms of action is provided by the case study described in Chapter 5. Here, the aim is to detect relevant exposures implicated in the exposure-outcome associations in the context of exposome-wide analyses. This involves screening the high-dimensional dataset characterising the urban exposome to first reduce the complexity by selecting the relevant variables for the outcome, and ultimately estimating their causal effects to quantify their impact on health. Knowledge about the exposures implicated in the reporting of headache provides important insights into potential mechanisms of actions to be targeted in

future studies (Chapter 5).

These considerations about study design, hypothesis framework, statistical methods, and critical interpretation of the results are closely interconnected and thoroughly contribute to understanding mechanisms of action in studies investigating the health effects of environmental exposures. The most relevant challenges related to the analysis of this data are discussed in the following paragraphs.

Optimising available exposure data is a critical step towards the effective conduct of epidemiological studies and interpretation of their results

An important aspect contributing to the effective conduct of an epidemiological study involves optimising available exposure data to enhance its informativeness for specific purposes. Depending on the study, this step may involve generating multiple metrics for the exposure of interest to be used in sensitivity analyses to assess the robustness of the results and facilitate their interpretation, particularly in scenarios where the mechanisms of action are uncertain. Another critical step involves pre-processing exposure data to conduct an initial description of the exposures and their characteristics, which includes, e.g., detecting underlying data structures and correlations, determining the best approach for handling missing values, and more.

In the context of RF-EMF exposure, the cohort study of mobile phone use and health (COSMOS) collects various self-reported information regarding the use of mobile phones and other wireless devices, including the proportion of time the participants use hands-free devices (Schüz et al., 2011). This information enables to adjust call-time according to the proportion of hands-free use reported by the participant to better approximate the true RF-EMF exposure to the head (Goedhart et al., 2015).
Depending on the available exposure data, multiple exposure metrics related to RF-EMFs can be obtained and used in sensitivity analyses to assess the robustness of the results of a particular study. This is the case for the strategy followed in Chapter 2. In particular, regarding RF-EMF exposure, we relied on self-reported duration of voice calling as reported by participants and voice-call duration obtained from network operators, in addition to regression calibrated values. These were estimated for each participant in the cohort as a combination of operator-recorded and self-reported call-time to improve the estimation of the exposure by reducing recall bias (Reedijk et al., 2023). Regression calibration methods are widely applied across several exposure domains to produce more insightful exposure-outcome relationships while accounting for exposure measurement error and misclassification (Bennett et al., 2017; Reedijk et al., 2023; Spiegelman, 2013).

To achieve an integrated radiofrequency electromagnetic fields (RF-EMF) dose assess-

ment in epidemiological studies and represent as much as possible the exposure levels encountered by individuals in their daily life, it is advisable to consider integrative approaches to quantify the exposure from the use of different electronic devices.
This is the case of the integrated exposure model (IEM), which represents a flexible tool to estimate weekly doses of RF-EMFs (measured in mJ/kg/week) in large epidemiological studies (van Wel et al., 2021). The IEM considers source-specific attributes, including output power and distance, personal characteristics such as height and weight of the user, and ultimately various usage patterns. Several sources of exposure can be included in the IEM, and the dose, depending on the emitting sources, can be calculated by targeting specific body organs or tissues (Cabré-Riera et al., 2022). Call duration on mobile and cordless phones was included as input data for the IEM in Chapter 2, as they were previously identified as main contributors to the target organ for headache, that is the brain (Cabré-Riera et al., 2022; van Wel et al., 2021).
Based on these considerations and through the optimisation of the available exposure data in COSMOS, we produced a comprehensive set of exposure metrics as a proxy for RF-EMF exposure, which were then used to further strengthen the main findings and their interpretation (Chapter 2).

Another aspect relevant to the effective conduct of the study, that may be overlooked, is the preliminary processing of exposure data. This step aims at optimising the available information before moving to the modelling of exposure-outcome relationships. Depending on the complexity of exposure data, this process does not come without challenges. Particularly in the context of exposome-wide analyses, pre-processing of exposure data represents an arduous and time-consuming yet essential aspect of the study, that aims to facilitate the subsequent analyses and interpretation of findings. This procedure encompasses various stages, typically including evaluating the skewness of exposures to meet the assumptions of statistical analyses and the use of different scales, exploring patterns (also related to existing correlations and missing data), aggregating exposures and calculating scores, and defining optimal buffers for neighbourhood-level exposures, among others.

Environmental exposure data often show non-negative values and right-skewness, which may require, e.g., log-transforming the exposures to approximate the normal distribution of their residuals. In the case of a substantial number of zeros on specific exposures, it is important to determine whether they correspond to absence of exposure to a particular chemical or undetected values, in which case the zeros may be replaced by predefined constant values. Alternatively, methods to deal with zero-inflated exposures (i.e. skewed variables with many zeros) can be applied (Lambert, 1992; K. H. Lee et al., 2023). Regarding how to handle missing values, multiple strategies are available

to explore the underlying patters (*Harrison E, Drake T, Pius R (2023). Finalfit: Quickly Create Elegant Regression Results Tables and Plots When Modelling. R Package Version 1.0.7*, 2023; Tierney & Cook, 2023). In the studies included in this thesis, multivariate imputation by chained equations (MICE) was frequently used to impute missing covariates or exposures, or both (Chapter 2, Chapter 4, Chapter 5) (Azur et al., 2011; Buuren & Groothuis-Oudshoorn, 2011). However, MICE users should be aware that, given the absence of accepted approaches to combine results from multiple imputed datasets following the imputation when using advanced statistical and machine learning methods, alternative strategies to Rubin's rule must be considered. These may include averaging imputed values across generated datasets (Chapter 5) or selecting the first or last imputed dataset, among others, although the existing literature offers no clear indications or preferred approaches for handling missing data in the high-dimensional settings typical of exposome research.

As part of the pre-processing of exposure data, especially in complex exposome research scenarios, it is recommended to conduct an exploration of the exposure data, which may include an initial screening of the exposures to detect particular data structures, visualise the variability present in the dataset, and identify potential extreme values or influential data points. This exploration involves the use of unsupervised techniques, such as principal component analysis, network and cluster analysis, to identify underlying patterns in the data without referring to the outcome of interest. An example is provided in Chapter 4, where K-means clustering is employed to classify participants into three clusters of air pollution exposure (low, moderate, high), ensuring that participants within the same group are as similar as possible. The results from this classification can be used to identify subgroups of individuals and compare participants between groups with respect to their characteristics.
Regarding the identification and management of outliers, winsorising and trimming offer two distinct solutions to mitigate the impact of potential extreme values (Ramsey & Ramsey, 2007; Rivest, 1994). Winsorising adjusts values beyond specified percentiles to match those percentiles, while trimming removes a percentage of the highest and lowest extreme values from a dataset. In either case, sensitivity analyses should be conducted to assess the robustness of results to different cutoff levels (B. K. Lee et al., 2011). Of note, trimming is often used in propensity score analysis to reduce the impact of relatively small and large weights on effect estimation, applied at both the upper and lower percentiles (i.e. symmetric trimming) of the weights' distribution (Chapter 4).

Another useful exploratory analysis involves obtaining pairwise correlation coefficients between all exposures in the dataset (correlation analysis). This step aims to identify high correlation structures, which should be addressed to prevent issues related to

(multi)collinearity or avoid exposure information redundancy in the subsequent statistical analyses. Using the R package *rexposome* is encouraged (Hernandez-Ferrer et al., 2022) to efficiently calculate correlation coefficients considering each exposure pair's nature, and facilitate visualisation of the correlation within the exposure data through circos and matrix plots as shown in Chapter 5.

A pluralistic approach is warranted to assess the overall health effect of multiple simultaneous and/or correlated exposures

In the analysis of environmental factors, one frequently comes across scenarios where multiple exposures occur simultaneously and, in many cases, these exposures show strong correlations (Carrico et al., 2015; García-García et al., 2021; Leal et al., 2012). Throughout this thesis, I often found myself facing this challenge.
In this section, I reflect on the approaches proposed across the different chapters to tackle the analysis of multiple exposures occurring simultaneously and, when necessary, I recommend strategies to address (multi)collinearity. Within the regression framework, (multi)collinearity arises when two or more exposures are highly correlated (i.e. the absolute magnitude of the observed correlation coefficient is 0.90 or more (Schober et al., 2018)), and the correlation structure affects the precision of the estimates and related standard errors, making it challenging to disentangle the individual effects of each exposure.

In the context of RF-EMFs, a possible solution to address the analysis of multiple exposures occurring simultaneously is represented by the use of an integrated approach (Chapter 2). Specifically, the integrated exposure model (IEM) incorporates multiple exposure sources into one single dose, which otherwise would need to be included in the same model as mutually adjusted exposures (co-exposures), with potential issues arising from strong correlations.
The IEM is designed to accommodate numerous other sources of RF-EMF exposure which, depending on the available exposure data, may include tablets, laptops, smartwatches, Wi-Fi routers, and far-field exposure, among others (van Wel et al., 2021).
However, when it comes to the assessment of voice calling and texting, a different scenario emerges as texting produces negligible amount of RF-EMF exposure resulting in a null dose from the IEM. As a result, the approach proposed in Chapter 2 consisted of including voice calling and texting in the same statistical model as co-occurring exposures, and this exposure construct is justified given that the correlation between the two is moderate.
In this respect, by comparing the confidence intervals of the estimates produced by logistic regression for the single-exposure models and those from the mutually adjusted model, we observed that the confidence interval widths of the estimates in the mutually

adjusted model did not increase compared to those from the single-exposure models. Results from the single and two-exposure models were comparable in terms of precision of their estimates, thus suggesting that in this scenario the moderate correlation did not affect the final results of the mutually adjusted model. In this regard, it is important to note that the strong correlation between exposures does not always imply that the regression estimates will be inflated and the standard errors biased (Bellavia et al., 2019).

A different scenario arises when it comes to the analysis of a mixture of air pollutants and overall mortality (Chapter 4). In studies concerning air pollution exposure, highly correlated pollutants are often encountered within the mixture, and traditional regression methods can fail to produce reliable results. As a consequence, researchers in environmental epidemiology have traditionally considered one exposure at a time, or at most two exposures, in their models to reduce complexity and better isolate the effects of individual pollutants on health outcomes (Dominici et al., 2010; Levy et al., 2014; Winquist et al., 2014).
However, in such scenarios, assessing the individual contributions of each component within the mixture separately, without accounting for other correlated exposures, could result in biased estimates (Correia & Williams, 2019). Therefore, evaluating the overall effect of multiple exposures becomes necessary, and pluralistic approaches are warranted (Dominici et al., 2010; Taylor et al., 2016; Vandenbroucke et al., 2016).

To assess the overall mixture effect and identify the main contributors within the mixture while accounting for the strong correlations, an approach is proposed in Chapter 4, which I briefly outline below.
First, following an inspection of the correlation coefficients calculated between the components of the mixture, the impact of multicollinearity of multiple regression estimates can be assessed by calculating variance inflation factors (VIFs).
The VIF is a common measure employed in regression analysis to identify coefficients affected by strong correlations between exposures and other independent variables in the model. As a rule of thumb, a VIF exceeding 10 indicates severe collinearity necessitating correction, which typically results in the exclusion of the problematic exposure(s) (*Variance Inflation Factor - an Overview | ScienceDirect Topics*, n.d.).
Second, by using a combination of methods, extracting meaningful information from the mixture becomes feasible by accounting for multicollinearity (Carrico et al., 2015; Lampa et al., 2014). Specifically, the approach described in Chapter 4 in the context of air pollution exposure consists in applying boosted regression trees (BRT) and weighted quantile sum (WQS) regression to gain insights about the mixture-outcome relationship, including interactions and nonlinearities.
BRT is an ensemble method based on decision tree algorithms and boosting methods

designed to estimate exposure variables' relative influence (or contribution) on a given outcome. In particular, BRT relies on regression trees to establish a relationship between a response variable and its predictors through recursive binary splits, and boosting to adaptively combine multiple models to enhance predictive performance.
An important strength of BRT models lies in their ability to identify two-way or higher-order interactions while relaxing assumptions of unidirectionality and linearity by using H-statistics which, for any pair of exposures, calculate the fraction of variance not captured by the sum of the two fitted response functions (Elith et al., 2008; Lampa et al., 2014).
On the other hand, WQS regression is designed to assess the overall mixture effect by building a single index estimated as a weighted linear combination of the exposures, which is robust to multicollinearity and can accommodate confounders. The weighted index can be interpreted as the joint effect of the mixture on the outcome.
In addition, WQS regression directly provides an estimate of the relative percent contribution of each exposure within the mixture to facilitate the identification of the most relevant contributor(s) (Carrico et al., 2015).
It is important to note that WQS regression makes an important assumption regarding unidirectionality (either positive or negative) of the effect of all exposures within the mixture on the outcome to avoid the reversal paradox (Tu et al., 2008), and therefore it should be applied only in situations where potential mechanisms of action have been identified and the effect direction of the exposures is known (Stafoggia et al., 2017). In this regard, it is worth mentioning the Bayesian extension of WQS regression (BWQS), which relaxes the unidirectional assumption (Colicino et al., 2020), and the grouped WQS (GWQS) regression, which overcomes the single-index limitation of WQS regression by allowing the estimation (in terms of magnitude and direction of association) of a weighted index for each considered exposure group (Wheeler & Czarnota, 2016).

In the specific scenario described in Chapter 4, the VIF screening raised concerns regarding one air pollutant ($PM_{2.5\ absorbance}$) within the mixture, and based on results from BRT and WQS indicating the lowest relative contribution for $PM_{2.5\ absorbance}$, the latter was excluded from the analysis to limit the impact of multicollinearity on the subsequent analyses. Furthermore, WQS and BRT suggested that all components contributed to a positive linear association with overall mortality, with $PM_{2.5}$ identified as the most relevant contributor in the mixture-outcome association.

Previous studies relied on other strategies to evaluate the association between environmental mixtures and health outcomes, primarily using pensalised methods. These methods extend standard Ordinary Least Squares (OLS) by adding a penalty to the loss function, reducing collinearity's impact.

It is important to note that penalised approaches address slightly different questions from those explored in Chapter 4, as they operate a variable selection by shrinking coefficients towards zero, rather than assessing the overall mixture effect. Furthermore, for highly correlated data, shrinkage methods such as Elastic Net and LASSO may suffer from grouping effect (i.e., sets of predictors that are correlated may be either entirely included or excluded arbitrarily during the process of variable selection) and arbitrary selection of exposures (i.e., collinear features may be automatically removed to reduce redundancy within the dataset), which could hamper the interpretation of findings in studies exploring the health effects of environmental mixtures, resulting in misleading conclusions (Carrico et al., 2015; Zou & Hastie, 2005). Additionally, interpreting LASSO estimates is not straightforward because standard errors and confidence intervals are not provided, and researchers often have to rely on conventional regression or bootstrap techniques to address the uncertainty of parameter estimation (Tibshirani, 1996). Consequently, in contexts such as the one described in Chapter 4, penalised methods may be less preferable than methods designed to assess the overall exposure effect, e.g., WQS (Czarnota et al., 2015).
In this regard, it is worthy to mention that a novel implementation of WQS, namely the random subset extension of WQS (WQS_{RS}), provides robust parameter estimation in high-dimensional mixtures, also in scenarios characterised by a high correlation structure among the mixture components (Curtin et al., 2021).
Of note, an alternative to LASSO in complex-dimensional settings is provided by Horseshoe regression where the shrinkage prior distribution, whose shape gives the name to this method, is particularly effective in situations where the dataset is characterised by a large number of irrelevant variables and a few significant ones (Piironen & Vehtari, 2017).

In conclusion, by using a combination of methods developed to address complexity in mixture modelling, we accounted for the high correlation structure characterising an environmental mixture of air pollutants, which traditionally poses great challenges in epidemiological studies due to the risk of obtaining unstable and biased parameter and standard error estimates. Furthermore, this approach allowed to identify the so-called "bad actors" in the mixture-outcome association, where traditional regression methods would have struggled.

In other scenarios, due to the high-dimensional nature of exposure data occurring simultaneously, the increased level of complexity necessitates innovative approaches that cannot be solely based on mixture modelling but requires an additional step. This is the case of exposome-wide analyses.
In this context, the approach described in Chapter 5 can be followed: first, to reduce

the general level of complexity characterising the exposure data, it is recommended to apply, e.g., a feature selection algorithm to identify relevant exposures in relation to the outcome being investigated (Bellavia, 2023). Second, once a set of exposures has been determined, it is suggested to evaluate the correlation levels among the exposures selected, and depending on those, decide on the most appropriate strategy to pursue next. In this regard, it is worth noting that *all-relevant* feature selection methods (that is, methods that aim to identify all features containing information useful for prediction, rather than selecting a potentially smaller subset of features that minimises the error for a particular classifier) typically result in the inclusion of redundant features and, consequently, exhibit some levels of correlation. In such a scenario, multicollinearity requires attention and the approach outlined in the context of air pollution mixture may provide a possible strategy to characterise the exposures and overcome issues related to strong correlations.
In the next section, I reflect on possible approaches that can be adopted to estimate causal effects, and more generally assess causal relationships, in the context of multiple exposures occurring simultaneously.

Considerations regarding hypothesis framework, exposure-outcome pathways, and study design are crucial for transitioning from association to causation with greater confidence

Throughout this thesis, I consistently questioned whether the observed associations could be considered causally related. In this section, I reflect on this critical aspect of my research. First of all, do we need causal methods to draw causal inferences? Based on the results of this thesis, I would argue that, depending on the specific scenario, this is not a strict requirement.

The use of an appropriate analytical approach in its broader sense (thus not only limited to "causal methods") is essential, but it should be complemented with other equally important elements of the research. These certainly include pre-analytical considerations about hypothesis framework, potential exposure-outcome pathways, and a robust study design.
Furthermore, other aspects that should be clearly defined in epidemiological studies to allow the transition from association to causation include a clear specification of the exposure levels being compared in the study and the identification of an adequate comparison group (Dominici & Zigler, 2017).

A valuable tool available to researchers in epidemiology to visualise causal relationships is the directed acyclic graph (DAG), which we often incorporated into the analysis plans prior to commencing the actual studies comprising this thesis.

DAGs play an important role in identifying potential sources of bias and potential causal pathways between variables (Tennant et al., 2021), and have proven to be valuable in addressing problems such as confounding by co-exposure in the context of mixture modeling (Webster & Weisskopf, 2020).
However, it should be noted that, due to the high dimension of exposure data characterising exposome studies, the use of DAGs in such a scenario can quickly become highly challenging. In this context, alternative methods should be pursued, such as causal discovery, a promising technique to derive a causal model starting from available data when no prior knowledge about potential causal relationships is available (Zanga et al., 2022).

One of the criteria to establish causality with greater confidence in epidemiological studies is to assess whether the cause precedes the effect (Nowinski et al., 2022). In this regard, in cohort studies, participants' exposure status is determined at the beginning of the study (baseline), while the health outcomes are exhibited during the follow-up.
This distinctive characteristic, referred to as temporality according to the Bradford Hill criteria for causation (Hill, 1965), is a key element in evaluating causality, shared among all studies included in this thesis.
Other important elements to consider when assessing whether the observed association could reflect causality are the strength of the association and the evaluation of the exposure-response relationship (Chapter 2). In addition, to further strengthen the conclusions about potential causal relationships, it is recommended to evaluate whether removing a cause decreases the risk of the effect. This approach was shown in Chapter 2, where the risk of reporting headaches among participants in the COSMOS cohort was compared based on whether their RF-EMF exposure to the head was calculated with or without adjustment for the use of hands-free devices. This approach enabled us to argue against the existence of an effect of exposure to RF-EMFs, as no risk reduction was observed among users when considering the hands-free adjusted exposure metric. Furthermore, sensitivity analyses using different exposure metrics are recommended to assess whether results lead to the same conclusions (Chapter 2).

In other scenarios, such as when the exposure and outcome are subject to considerable fluctuations over time and the underlying mechanisms of action are uncertain, it is necessary to adopt a different approach (Chapter 3).
Here, temporality extends beyond evaluating exposure and outcome at only two time points. Participants require follow-up at multiple time points to be able to assess changes in exposure and outcome over time. Therefore, in this specific scenario, identifying potential causal relationships relies on careful considerations about the study design and the use of appropriate statistical techniques that allow to model the transition between

different states while considering the temporal progression.
With a certain level of confidence, these elements allowed us to exclude the biological and cognitive pathways and identify the most plausible underlying causal route for the time course of IEI-RF in the attributive hypothesis (Chapter 3).

Identification of a set of exposures relevant for the outcome and causal effect quantification in the analysis of complex-dimensional data

In the context of environmental exposures occurring simultaneously, which reflects what happens in real-world settings, the following approach can be pursued: first, to reduce the level of complexity within exposure data (i.e. to reduce the number of exposures for which there is an interest in estimating the causal effect), supervised variable selection techniques can be used to identify the exposures that are involved in the association with the outcome. In this regard, several options are available (which traditionally fall into three methodological categories: filter, wrapper, embedded), each with its advantages and limitations (Hancock et al., 2024; Jović et al., 2015; Uddin et al., 2019). Examples include information gain based on entropy calculation, recursive feature elimination and forward/backward selection, regularisation and random forest importance, and more. Additionally, variable selection methods have been extended to include hybrid, ensemble, and integrative approaches (Pudjihartono et al., 2022).
It is worth noting that, depending on the research question, a specific group of exposures sharing a common mode of action (i.e. environmental mixture) may have already been identified (Chapter 4).

In Chapter 5, a case study is provided in the context of the urban exposome of AMIGO in relation to reporting headache. Following the outlined approach, Boruta was used to identify the features relevant to the outcome. Boruta represents a powerful machine learning algorithm for the analysis of high-dimensional datasets designed to identify pertinent variables of complex-dimensional scenarios by taking into account interactions and nonlinear associations (Degenhardt et al., 2017; Kursa & Rudnicki, 2010).

To account for class imbalance due to low prevalence of headache in the study population, the approach proposed in Chapter 5 consisted in running the Boruta algorithm repeatedly (here, 250 times), and randomly sampling 85% of the minority group size (i.e. number of participants reporting headache at follow-up) without replacement in both majority and minority groups (i.e. participants without and with headache at follow-up, respectively) to obtain 250 balanced datasets (More & Rana, 2017). To determine which exposures in the dataset are most relevant for explaining the outcome, the features labelled as “important” by Boruta in at least 80% of the 250 iterations were selected.
A distinctive characteristic of feature selection methods such as Boruta is the aim to find

all features carrying information usable for prediction, following the so-called *all-relevant* feature selection strategy. In this regard, it is reasonable to expect that *all-relevant* methods result in the inclusion of features that may be redundant and display some level of correlation between the selected variables. In this scenario, multicollinearity should be addressed and the approaches described in the previous sections provide possible directions.

Once the relevant exposures in relation to the outcome of interest have been determined, the attention can shift towards estimating their effects to improve the causal understanding of the associations. However, how can the most appropriate statistical approach be determined in this context?
As previously argued, using causal methods is not *per se* a requirement and, most importantly, it does not imply that the observed effect is necessarily causally related to the exposure (Dominici & Zigler, 2017). However, in studies evaluating the health effects of mixtures, and even more in the context of exposome-wide analyses characterised by high-dimensional exposure data, sophisticated methods should be warranted to take into account the co-occurrence of exposures (Maitre et al., 2022).

To explore the health effects of environmental mixtures, we start from a simplified exposure-outcome scenario which involves a preselected set of exposures (air pollutants) and a well-defined, non-transient, outcome (mortality) (Chapter 4).
Once the mixture has been characterised (e.g., using the methods described earlier, e.g. WQS, BRT), the next step involves the estimation of the joint effect, that is the effect of each component within the mixture on the outcome while taking into account the simultaneous occurrence of the exposures (i.e. co-exposure), which reflects real-world exposure conditions. In this regard, multiple approaches can be pursued, and researchers should be aware that clear indications on the preferred course of action have not yet been established.

Williams and Crespi propose a versatile approach as an extension of the generalised propensity score (GPS), which allows estimation of an exposure-response surface that reflects the joint distribution of multiple continuous exposures in relation to an outcome (Williams & Crespi, 2020).
Specifically, the multivariate GPS method (mvGPS) generates stabilised inverse probability of treatment weights (IPTWs) assuming a multivariate normal distribution for the simultaneous exposures. An advantage of these weights is their ability to balance confounders and provide unbiased exposure–response estimates (Robins et al., 2000).
As argued by Dominici and Zigler, the evidence of causality should be assessed based on how closely the study resembles a randomised experiment and how deviations could

bias the obtained results (Dominici & Zigler, 2017). Propensity score-based techniques align with this direction as they aim to remove potential confounding between exposure and outcome returning valid estimates of the treatment effect that prove to be extremely valuable in estimating the causal effect of multiple continuous exposures in the context of observational and non-randomised studies.
Furthermore, the estimation of mvGPS weights has proved to be effective at reducing the impact of correlation between exposures and confounders, also in situations where high marginal exposure correlations are present (Williams & Crespi, 2020).
In such circumstances, the mvGPS weights should be checked and trimmed accordingly to exclude extreme weights' influence (B. K. Lee et al., 2011; Williams & Crespi, 2020). However, before relying on weight trimming to optimise propensity score weighting, the focus should be rather placed on improving propensity score model specification regarding, e.g., selection of variables, nonlinearities and interactions (Brookhart et al., 2006; B. K. Lee et al., 2011).

In our specific scenario, no extreme weights were identified in the distribution of propensity scores, and results obtained using different levels of trimming were consistent (Chapter 4). These findings further support the ability of mvGPS to deal with strong correlations, which often characterise environmental mixtures.
Of note, the current version of mvGPS is particularly appealing for its application in epidemiological studies given the possibility to specify multiple sets of confounders for each exposure of interest reflecting many real-world settings in which the confounders may actually differ across exposure variables (Williams & Crespi, 2020).
However, researchers should be aware that mvGPS is designed to handle continuous exposures under the assumption of normal distribution. This assumption, particularly in relation to environmental exposures, is often not valid thus representing a limitation of this method. Furthermore, more research should be conducted to assess the ability of mvGPS to achieve adequate balance in scenarios where more than two continuous exposures are evaluated. In this regard, the existing knowledge is insufficient and the recommendation to use data reduction or variable selection techniques to transform a high-dimensional problem to a scenario where a lower number of exposures are being considered applies, which again brings us back to a simplistic scenario that does not align with real-world complexities (Williams & Crespi, 2020).

A distinct approach is proposed in Chapter 5 to account for the co-occurrence of multiple exposures in the context of exposome-wide analysis. Here, the aim is to estimate the causal effect of each exposure separately adjusting for confounding by co-exposure. This approach develops within the potential outcomes (or counterfactual) framework. It consists in training causal forests to estimate the average treatment effect (ATE) and

corresponding standard error for each one of the exposures resulting from the feature selection process, under the assumption of unconfoundedness (Rosenbaum & Rubin, 1983).
Causal forests represent an extension of Breiman's random forests for the estimation of causal effects and can accommodate both continuous and binary exposures. Their distinctive characteristic is the estimation of propensity scores, which establishes conditions for robustness against confounding. As a result, causal forests estimate ATE under the assumption of absence of confounding (i.e. the treatment assignment is independent of the potential outcome conditional on the confounders) (Athey & Wager, 2019). Specifically, the ATE represents the average difference in potential outcomes in a sample where everyone is treated versus the same sample where everyone is untreated.
In scenarios where the treatment is continuous, causal forests effectively estimate an average partial effect, which quantifies the change in the expected outcome due to a one-unit change in the treatment, given unconfoundedness (Athey & Wager, 2019).
Furthermore, causal forests are particularly well-suited in scenarios where the treatment effect varies across different subgroups of the population. In this regard, an interesting feature of the algorithm is the estimation of conditional average treatment effects (CATEs). These represent the average difference in potential outcomes in a specific stratum of the population, where everyone in that stratum is exposed versus a scenario where everyone in the same stratum is unexposed (Jawadekar et al., 2023).
Interestingly, the estimation of CATEs with regard to the presence of headaches at baseline allowed us to identify a vulnerable subpopulation more susceptible to the effects of air pollution exposure and heat island effects with a higher risk of reporting headaches at follow-up compared to participants free of headaches at the onset of the study (Chapter 5).

In the specific scenario described in Chapter 5, the estimated effects of each one of the exposures selected by Boruta with adjustment for confounding by co-exposure resulted in less precise effect estimates compared to the models without adjustment. Despite the efforts to address the extremely problematic correlation levels between the exposures in our study, these findings suggest that, in situations where strong correlations occur, the covariate balancing propensity score method implemented in causal forests may fail to achieve the covariate balancing property, and different approaches to estimate propensity scores in such a situation should be explored.

Despite both causal forests and mvGPS being developed as part of causal framework to estimate causal effects in observational studies, there is a substantial difference in the rationale behind the use of the two approaches in this thesis: while mvGPS jointly estimate the effect of multiple continuous exposures on the outcome, causal forests

estimate the independent effect of each exposure on the outcome accounting for confounding by co-exposure. In other words, in the forests we consider the possibility that exposures other than the exposure for which the causal effect is being estimated may act as confounders, potentially leading to inappropriate conclusions about causality if not accounted for.
This aspect appears relevant particularly in exposome studies where, due to the high complexity of exposure data, the (temporal) relationships between variables at baseline (either exposures or potential confounders) are not clearly defined.
In this regard, a substantial inconsistency in defining confounders in exposome research should be acknowledged, and whether factors related to social determinants of health such as gender, education, ethnicity, income should be considered exposures or confounders to avoid spurious results (Neufcourt et al., 2022). Concerning this, it should be noted that the approach adopted in Chapter 5 is in principle "agnostic", meaning that all the environmental exposures, individual-level (social) determinants of health, and neighbourhood-level factors are regarded as exposures in Boruta, with no specific assumptions made regarding temporal or causal relationships between them.

There are policy implications that can be derived from the studies conducted as part of this work

With regard to RF-EMF exposure and associated health effects, it should be acknowledged that, based on findings from Chapter 2, RF-EMF exposure from mobile phone use is unlikely to be the cause of headaches and migraines that were observed among mobile phone users. As a result, no need arises for implementing regulations to limit exposure to RF-EMFs compared to those already in place.
While this finding is certainly reassuring, symptoms reported by participants are real and disabling, and as such, they deserve attention. Consequently, given the significant burden of headaches in the population and the widespread mobile phone use, further investigation into other aspects of mobile phone use than RF-EMF exposure, such as recurring patterns of behaviour among users and other factors that could have mediated the effect that we observed for texting, is warranted to prevent health effects.

Findings from the study discussed in Chapter 3 investigating the time course of attribution of health complaints to RF-EMFs lend support to the attributive hypothesis. This hypothesis suggests that individuals may attribute symptoms to RF-EMF exposure to elucidate a health issue and alleviate uncertainty about its underlying cause, or offer an explanation for a missed diagnosis. Unlike the biological and cognitive hypotheses, which would advocate, respectively, for revising regulations to limit RF-EMF exposure and for improving public communication on RF-EMF topics, the attributive hypothesis does not inherently call for any specific policy actions given that the mechanism seems to elude the control of both scientific community and institutions.

The investigation of air pollution exposure and its associated health effects presented in Chapter 4 highlights the prominent role of $PM_{2.5}$ as primary contributor within the mixture. In this regard, current policies often address single pollutants separately. However, a thorough understanding of causality, achieved by considering the co-occurrence of multiple pollutants, might prompt the development of more targeted regulatory approaches. Therefore, the strategy adopted in our analysis provides a more comprehensive approach to the study of causal mechanisms associated with air pollution exposure. As such, it can serve as an example for future research beyond air pollution aiming at understanding the intricate interplay between environmental exposures and human health by considering the health effects of environmental mixtures rather than relying on a "one-at-a-time chemical approach".

Chapter 5 shows a possible strategy to tackle complexity in exposome-wide analyses following a two-stage approach: identifying a set of exposures relevant for the outcome and then quantifying their causal effect. Our findings suggest that air pollution and urban temperature measures are implicated in reporting headaches in the population. As such, these insights serve as a first screening to understand what factors are implicated in the reporting of symptoms in the population. No direct policy implications can be derived from this exercise. However, by shedding light on the potential adverse effects of the urban environment on health, we emphasise the necessity of a comprehensive assessment of common urban stressors to prevent health issues.

Concluding remarks

Assessing the health impact of environmental exposures poses several challenges, ranging from methodological aspects related to study design, data collection, and statistical methods to practical considerations such as resource limitations and logistical constraints.
The aim of the thesis was to propose and reflect on approaches for improving the identification and interpretation of underlying mechanisms of action for environmental exposures commonly encountered in everyday life and facilitating the establishment of causal relationships. Throughout the thesis, I showed that different approaches can be used to tackle complexity and derive conclusions across a range of scenarios. The common factor among these approaches was the use of data from large prospective epidemiological studies.

Some major challenges have been addressed in this thesis. These concern the identification of underlying mechanisms of actions, particularly concerning RF-EMF and air pollution exposure. Furthermore, aspects related to optimising available exposure data to efficiently analyse and interpret exposure-outcome associations, including pre-processing to reduce complexity in (high-dimensional) exposure data, were discussed. Finally,

strategies to tackle multiple exposures occurring simultaneously and issues related to multicollinearity in the context of co-occurring exposures were presented, along with approaches to estimate causal effects across different scenarios of complexity.

In scenarios where the mechanisms of action are uncertain, it is essential to define a hypothesis framework regarding the pathways potentially involved in the exposure-outcome association and make considerations about pre-analytical aspects of the study with particular attention to its design. This approach is recommended to reduce the likelihood of unexpected findings and make interpreting results more straightforward. In other scenarios, where complexity is further enhanced by the presence of, e.g., strong correlations and high-dimensional exposure data, it is recommended to first reduce complexity and then estimate the causal effects.

The findings of this thesis shed light on various areas necessitating further investigation. Understanding how RF-EMF exposure may affect health requires a comprehensive approach and, in future studies, employing an integrative model that considers various RF-EMF sources individuals encounter daily is essential. Nevertheless, this approach may require continuous updates to keep up with rapid technological advancements and changes in exposure-related user behaviours.
When analysing environmental exposures occurring simultaneously, it is crucial to shift from the traditional "one-at-a-time exposure approach" to evaluating the entire mixture to understand the joint impact of its components, thus reflecting real-world conditions. Strong correlations, interactions, and nonlinearities among these components introduce several methodological challenges that must be overcome to ensure accurate and reliable conclusions. Furthermore, future studies should prioritise incorporating the time-varying nature of exposures and mixtures when evaluating individual risk factors over a lifetime, as these may have different impacts at different stage of individuals' lives.
Finally, more research should be conducted on estimating causal effects in the context of high-dimensional mediation analysis to account for multiple mediators and on better defining how confounders should be identified and addressed in complex-dimensional settings typical of, e.g., exposome-wide studies. All of these factors highlight the need for further research to develop innovative analytical methods, or adapt existing ones, to effectively answer current and future research questions.

In conclusion, based on the results presented in this thesis, a comprehensive and pluralistic approach to tackle real-world complexity is warranted and, most importantly, no one-size-fits-all strategy can be identified in epidemiological research. While there may not be a perfect method to proceed, curiosity and a willingness to explore alternative methods are crucial in advancing the understanding of complex phenomena such as

those characterising the health impact of environmental exposures.

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Appendices

Summary

Throughout their life, individuals are exposed to numerous environmental factors that may affect their health and well-being. Among those, air pollution and radiofrequency electromagnetic fields (RF-EMFs) represent common exposures that are widespread in the environment.

The main objective of this thesis was to propose informative approaches for the analysis of environmental factors commonly encountered in everyday life in relation to health outcomes, using data from prospective studies. These approaches aimed to provide valuable insights into exposure-outcome associations, including potential mechanisms of action and underlying causal pathways, in order to prevent harmful health effects. For this purpose, data from large prospective epidemiological studies were analysed using a combination of advanced statistical techniques and machine learning methods, including multi-state Markov models, weighted quantile sum regression and boosted regression tree models, Boruta and causal forests, and extensions of regression techniques based on propensity score estimation, such as the generalised propensity score for single exposures and its multivariate version.

This thesis had the following specific aims:

i. To extract meaningful insights and draw conclusions regarding exposure-outcome associations in scenarios where the mechanisms of action are uncertain and/or difficult to determine, by exploring different potential pathways while optimising available exposure data;
ii. To explore the temporal dynamics of health outcomes characterised by considerable fluctuations over time, by analysing data across multiple time points, accounting for time-dependent risk factors;
iii. To explore an environmental mixture and determine the causal effect of its components on health, within a simplified exposure-outcome scenario involving a preselected set of exposures and mortality as endpoint;
iv. To identify a relevant set of exposures and estimate their causal effects in studies assessing the impact of multiple exposures occurring simultaneously on health, in an exposure-outcome scenario characterised by high-dimensional exposure data typical of exposome-wide studies.

To achieve the objectives of the thesis, data from the cohort study of mobile phone use and health (COSMOS), LIFEWORK, and the Dutch occupational and environmental health cohort study (AMIGO) were analysed.
COSMOS (n=~250,000) is an international prospective cohort study comprising data collected across six European countries (Denmark, Finland, Sweden, the Netherlands, the UK, and France) established to investigate potential health effects from long-term use of mobile phones and other wireless technologies.
LIFEWORK (n=~90,000) is a large federated prospective cohort in the Netherlands representing the Dutch contribution to COSMOS. The aim of LIFEWORK is to quantify the health effects of numerous occupational and environmental exposures, with a specific focus on assessing RF-EMF exposure from mobile phones and other wireless devices.
AMIGO (n=~14,000) is the Dutch occupational and environmental health cohort study, and represents one of the subcohorts included in LIFEWORK. In AMIGO, we investigate occupational and environmental determinants of diseases and well-being, including RF-EMF exposure, relying on a multidisciplinary and life course approach.

In **Chapter 2**, pooled data from the Dutch and UK cohorts of COSMOS (N=78,437) were analysed to explore two potential exposure-outcome pathways in relation to mobile phone use and the occurrence of headaches. Results from multivariable logistic regression models showed that mobile phone use for calling and texting at baseline was associated with headaches at follow-up. In the mutually adjusted model for both call-time and texting, we observed considerably attenuated risk estimates for call-time, while associations with texting were still strong and robust to adjustment, with a clear exposure-outcome relationship. These results suggested that, due to the negligible exposure to RF-EMFs from texting, mechanisms other than RF-EMFs (e.g., lifestyle, other exposures, or behavioural factors associated with mobile phone use) were responsible for the increased risk of headache that we observed among mobile phone users. Given the significant burden of headaches in the population and the widespread mobile phone use, further investigation into other aspects of mobile phone use than RF-EMF exposure is warranted to prevent health effects.

In **Chapter 3**, we explored the temporal dynamics of attribution of health complaints to RF-EMFs (IEI-RF) in the subcohort of AMIGO (N=892). We assessed factors related to developing, maintaining, or discarding IEI-RF over the course of 10 years by modelling the process in which participants move through a series of states of IEI-RF with multistate Markov models. Furthermore, we applied logistic regression to prospectively explore predictors of electromagnetic hypersensitivity without the condition of attributing health complaints to RF-EMF exposure (EHS). Results showed that prevalence of IEI-RF was generally low and remained stable over time. Interestingly, over 10 years of fol-

low-up, we observed a high probability of not attributing symptoms to RF-EMF exposure anymore, which suggested that IEI-RF may be a more transient condition than previously assumed. Finally, RF-EMF perceptions, non-specific symptom reporting, and sleep disturbances at baseline were predictive of the notion of being EHS at 10 years follow-up, regardless of whether reporting health complaints attributed to RF-EMF exposure.

In **Chapter 4**, we relied on a pluralistic approach to prospectively explore the relationship between a mixture of air pollutants ($PM_{2.5}$, PM_{10}, NO_2, $PM_{2.5\ absorbance}$, and oxidative potential) and mortality in LIFEWORK (N=86,882). We applied weighted quantile sum (WQS) regression and boosted regression trees (BRT) to identify the most relevant components within the mixture in relation to the outcome accounting for the strong correlations. Based on these results, we estimated a multivariate generalized propensity score (mvGPS) model to jointly estimate the causal effects of the pollutants on overall mortality. Results from WQS regression and BRT indicated that all components of the mixture contributed to a positive linear association with the outcome, with $PM_{2.5}$ identified as the most relevant contributor. Finally, results from the mvGPS model further highlighted the primary role of $PM_{2.5}$ within the mixture, strengthening the causal interpretation of air pollution effects on mortality. The strategy adopted in this study can serve as an example for future research beyond air pollution aiming at understanding the intricate interplay between environmental exposures and human health by considering the health effects of environmental mixtures rather than relying on a "one-at-a-time chemical approach".

In **Chapter 5**, we prospectively explored the urban component of the exposome of AMIGO (N=7,339) in relation to headaches by using a combination of machine learning techniques. We followed a two-stage approach where we first applied Boruta to identify relevant exposures in the exposome-outcome association, and then estimated causal forest to quantify the causal effect of these exposures on the occurrence of headache. Boruta selected five air pollutants (NO_2, NO_x, PM_{10}, silicon in PM_{10}, iron in $PM_{2.5}$) and one urban temperature measure (heat island effect) as factors contributing to the reporting of weekly headache at follow-up. The estimated causal effect of each exposure on weekly headache indicated positive associations for all exposures, with NO_2 displaying the largest effect. These results highlight the relevance of air pollution exposure and heat island effects in contributing to the reporting of weekly headache in AMIGO, and emphasise the necessity of a comprehensive assessment of common urban stressors to prevent health issues.

In **Chapter 6**, I presented the main findings of the studies comprising this thesis. Following this summary, I discussed the approaches proposed to identify underlying mechanisms of action and addressed the most relevant challenges encountered in the different

studies, highlighting advantages and limitations of the methods used, and providing policy implications and possible directions for future research.

Samenvatting

Gedurende hun leven worden individuen blootgesteld aan tal van omgevingsfactoren die hun gezondheid en welzijn kunnen beïnvloeden. Onder andere luchtverontreiniging en radiofrequente elektromagnetische velden (RF-EMV) vormen veelvoorkomende blootstellingen die wijdverspreid zijn in de omgeving.

Het hoofddoel van dit proefschrift was het voorstellen van informatieve benaderingen voor de analyse van omgevingsfactoren die vaak voorkomen in het dagelijks leven in relatie tot gezondheidsuitkomsten, met behulp van gegevens uit prospectieve studies. Deze benaderingen waren gericht op het verschaffen van waardevolle inzichten in de blootstelling-uitkomst associaties, inclusief potentiële werkingsmechanismes en onderliggende causale verbanden, om schadelijke gezondheidseffecten te voorkomen.
Met dit doeleind zijn data van grote prospectieve epidemiologische studies geanalyseerd met behulp van een combinatie van geavanceerde statische technieken en “machine learning” methodes, waaronder “multi-state Markov” modellen, “weighted quantile sum” (WQS) regressie en “boosted regression tree” (BRT) modellen, Boruta en “causal forests”, en uitbreidingen van regressietechnieken gebaseerd op “propensity score” schatting, zoals de “multivariate generalised propensity score” (mvGPS) voor enkele blootstellingen en de multivariate versie daarvan.

Dit proefschrift had de volgende specifieke doelstellingen:

i. Het verkrijgen van betekenisvolle inzichten en conclusies trekken over blootstelling-uitkomst associaties in scenario’s waar de werkingsmechanismen onzeker en/of moeilijk te bepalen zijn, door verschillende mogelijke mechanismen te verkennen terwijl de beschikbare blootstellingsdata geoptimaliseerd worden;
ii. Het verkennen van de temporele dynamiek van gezondheidsuitkomsten gekenmerkt door aanzienlijke fluctuaties over de tijd, door data over meerdere tijdspunten te analyseren en tijdsafhankelijke risicofactoren in acht te nemen;
iii. Het verkennen van een mengsel van omgevingsfactoren en het vaststellen van causale effecten van de componenten op de gezondheid, binnen een vereenvoudigd blootstelling-uitkomst scenario met een voorgeselecteerde set blootstellingen en sterfte als eindpunt;
iv. Het identificeren van een relevante set blootstellingen en het schatten van hun causale effecten in studies die de impact van meerdere gelijktijdig voorkomende

blootstellingen op de gezondheid evalueren, in een blootstelling-uitkomst scenario gekenmerkt door hoog-dimensionale blootstellingsdata die typisch zijn voor exposoom-brede studies.

Om de doelstellingen van het proefschrift te bereiken zijn data geanalyseerd van de cohortstudie naar mobiele telefoongebruik en gezondheid (COSMOS), LIFEWORK, en het Nederlandse Arbeid, Milieu en Gezondheid Onderzoek (AMIGO).

COSMOS (n=~250,000) is een internationale prospectieve cohortstudie met gegevens verzameld in zes Europese landen (Denemarken, Finland, Zweden, Nederland, het Verenigd Koninkrijk, en Frankrijk)die is opgezet om mogelijke gezondheidseffecten van langdurig mobiele telefoongebruik en andere draadloze technologieën te onderzoeken.
LIFEWORK (n=~90,000) is een groot gefedereerd prospectief cohort in Nederland dat de Nederlandse bijdrage aan COSMOS vertegenwoordigt. Het doel van LIFEWORK is het kwantificeren van gezondheidseffecten van talrijke beroeps- en omgevingsblootstellingen, met een specifieke focus op het evalueren van RF-EMV blootstelling door mobiele telefoons en andere draadloze apparaten.
AMIGO (n=~14,000) is de Nederlandse cohortstudie naar arbeid, milieu en gezondheid, en vormt één van de subcohorten die zijn opgenomen in LIFEWORK. In AMIGO worden beroeps- en omgevingsdeterminanten van ziekten en welzijn onderzocht, inclusief RF-EMV blootstelling, met behulp van een multidisciplinaire en levensloopbenadering.

In **hoofdstuk 2** werden gepoolde gegevens van de Nederlandse en Britse cohorten van COSMOS (N=78,437) geanalyseerd om twee potentiële blootstelling-uitkomst mechanismen in relatie tot mobiele telefoongebruik en het optreden van hoofdpijn te verkennen. Resultaten van de multivariabele logistische regressiemodellen lieten zien dat het gebruik van mobiele telefoons voor bellen en sms'en op baseline was geassocieerd met hoofdpijn bij follow-up.
In het wederzijds gecorrigeerde model voor zowel beltijd als sms'en werden aanzienlijk verzwakte risicoschattingen voor beltijd geobserveerd, terwijl associaties met sms'en sterk bleven en robuust voor correctie, met een duidelijke blootstelling-uitkomst relatie. Deze resultaten suggereerden dat, vanwege de verwaarloosbare blootstelling aan RF-EMV door sms'en, andere mechanismen dan RF-EMV (bijvoorbeeld leefstijl, andere bloostellingen, of gedragsfactoren geassocieerd met mobiele telefoongebruik) verantwoordelijk waren voor het verhoogde risico op hoofdpijn dat we observeerden onder mobiele telefoongebruikers. Gezien de significante ziektelast van hoofdpijn in de bevolking en het wijdverbreide gebruik van mobiele telefoons is verder onderzoek naar andere aspecten van mobiele telefoongebruik dan RF-EMV blootstelling gerechtvaardigd om gezondheidseffecten te voorkomen.

In **hoofdstuk 3** hebben we de temporele dynamiek van de toeschrijving van gezondheidsklachten aan RF-EMV (IEI-RF) in het AMIGO subcohort (N=892) onderzocht. We beoordeelden factoren gerelateerd aan het ontwikkelen, behouden, of loslaten van IEI-RF gedurende 10 jaar door met "multi-state Markov" modellen het proces te modelleren waarin deelnemers door een reeks staten van IEI-RF bewegen. Verder hebben we logistische regressie toegepast om prospectief voorspellers van elektrohypersensitiviteit zonder het toeschrijven van gezondheidsklachten aan RF-EMV blootstelling (EHS) te verkennen.
De resultaten toonden aan dat de prevalentie van IEI-RF over het algemeen laag was en stabiel bleef over de tijd. Interessant genoeg observeerden we over 10 jaar follow-up een hoge waarschijnlijkheid om de symptomen niet meer aan RF-EMV blootstelling toe te schrijven, wat suggereerde dat IEI-RF een meer voorbijgaande aandoening is dan voorheen werd aangenomen. Ten slotte bleken RF-EMV percepties, het rapporteren van niet-specifieke symptomen, en slaapverstoringen op baseline voorspellend te zijn voor EHS na 10 jaar follow-up, ongeacht of gezondheidsklachten werden gerapporteerd die werden toegeschreven aan RF-EMV blootstelling.

In **hoofdstuk 4** hebben we een pluralistische benadering toegepast om de relatie tussen een mengsel van luchtverontreinigende stoffen ($PM_{2.5}$, PM_{10}, NO_2, $PM_{2.5}$ absorptie, en oxidatief potentieel) en sterfte prospectief te verkennen in LIFEWORK (N=86,882). We hebben "weighted quantile sum" (WQS) regressie en "boosted regression trees" (BRT) toegepast om de meest relevante componenten binnen het mengsel in relatie tot de uitkomst te identificeren, rekening houdend met de sterke correlaties. Op basis van deze resultaten hebben we een "multivariate generalized propensity score" (mvGPS) geschat om gezamenlijk de causale effecten van de verontreinigende stoffen op algehele sterfte te schatten. Resultaten van de WQS regressie en BRT duidden aan dat alle componenten van het mengsel bijdroegen aan een positieve lineaire associatie met de uitkomst, waarbij $PM_{2.5}$ werd geïdentificeerd als meest relevante component. Ten slotte benadrukten de resultaten van het mvGPS model de primaire rol van $PM_{2.5}$ binnen het mengsel, wat de causale interpretatie van luchtverontreinigingseffecten op sterfte versterkte. De in deze studie toegepaste strategie kan als voorbeeld dienen voor toekomstig onderzoek, ook buiten luchtverontreiniging, om de ingewikkelde wisselwerking tussen omgevingsblootstellingen en gezondheid te begrijpen door de gezondheidseffecten van een mengsel van omgevingsfactoren in acht te nemen in plaats van te vertrouwen op een "één-voor-één benadering" voor chemische stoffen.

In **hoofdstuk 5** onderzochten we prospectief de stedelijke component van het exposoom van AMIGO (N=7,339) in relatie tot hoofdpijn met gebruik van een combinatie van "machine learning" technieken. We hebben een tweestappenbenadering gevolgd waarbij

we eerst Boruta hebben toegepast om de relevante blootstellingen in de exposoom-uitkomst associatie te identificeren, waarna we “estimated causal forest” hebben gebruikt voor het kwantificeren van het causale effect van deze blootstellingen op het optreden van hoofdpijn.
Boruta selecteerde vijf luchtverontreinigende stoffen (NO_2, NO_X, PM_{10}, silicium in PM_{10}, ijzer in $PM_{2.5}$) en één maat voor stedelijke temperatuur (hitte-eiland effect) als factoren die bijdragen aan het rapporteren wekelijkse hoofdpijn bij follow-up. Het geschatte causale effect van elke blootstelling op wekelijkse hoofdpijn toonde positieve associaties voor alle blootstellingen, waarbij NO_2 het grootste effect vertoonde. Deze resultaten benadrukken de relevantie van bloostelling aan luchtverontreiniging en hitte-eiland effecten in de bijdrage aan het rapporteren van wekelijkse hoofdpijn in AMIGO en de noodzaak van een uitgebreide evaluatie van veelvoorkomende stedelijke stressoren om gezondheidsproblemen te voorkomen.

In **hoofdstuk 6** heb ik de hoofdbevindingen van de in dit proefschrift opgenomen studies gepresenteerd. Na deze samenvatting besprak ik de voorgestelde benaderingen om onderliggende werkingsmechanismen te identificeren en ging ik in op de meest relevante uitdagingen die zijn aangetroffen in de verschillende studies, met nadruk op de voordelen en beperkingen van de gebruikte methoden, en verschafte ik beleidsimplicaties en mogelijke toekomstige onderzoeksrichtingen.

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Curriculum Vitae

Eugenio Traini was born on November 6, 1988, in Rome, Italy. He obtained a Bachelor's degree in Statistics from the University of Rome "La Sapienza" in 2013. Under the supervision of Prof. Viviana Egidi, his dissertation in Social Statistics examined the determinants of inequalities in functional disability using data from the European Union Statistics on Income and Living Conditions (EU-SILC).

In 2015, he moved to Bologna to pursue a Master's degree in Statistics at Alma Mater Studiorum, University of Bologna. During the final phase of the Master's program, he joined the Clinical Epidemiology and Biostatistics unit at the Institute for Maternal and Child Health (IRCCS "Burlo Garofolo") in Trieste. There, supervised by Prof. Paola Rucci (University of Bologna) and Dr. Valentina Rosolen (IRCCS "Burlo Garofolo"), he investigated the health effects of mercury exposure from fish consumption in a prospective mother-child cohort living in northeastern Italy using a quantile-regression approach, culminating in his thesis and graduation in 2018.

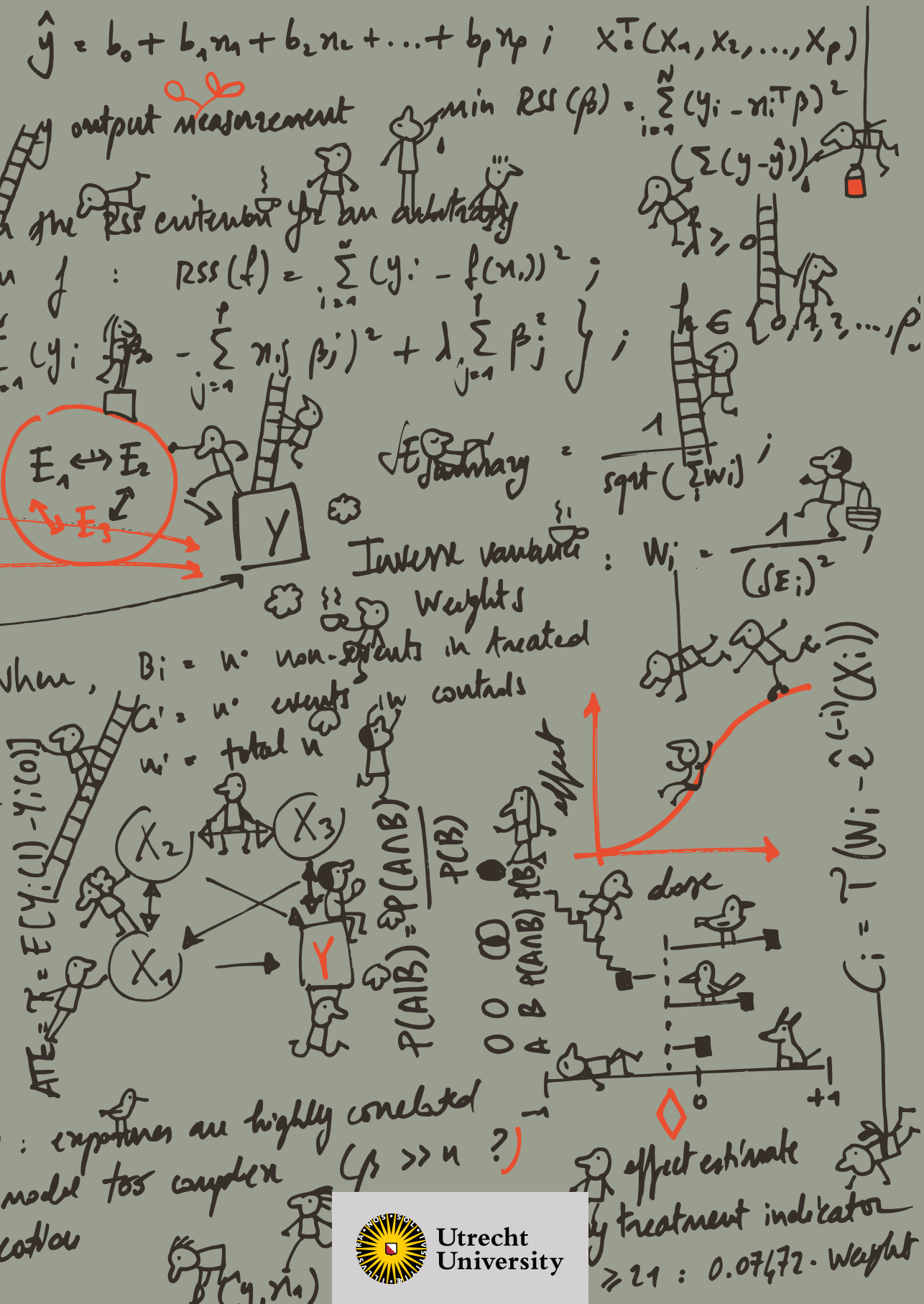
Following his Master's degree, Eugenio continued at IRCCS "Burlo Garofolo" as a statistician, collaborating on various projects with fellow statisticians, epidemiologists, and clinicians, while also supervising medical students in the analysis of clinical data. In 2020, he embarked on a PhD in environmental epidemiology at the Institute for Risk Assessment Sciences (IRAS) in Utrecht, the Netherlands, under the supervision of Prof. Roel Vermeulen and Dr. Anke Huss. His PhD research focused on developing informative approaches for the analysis of environmental exposures and their health impacts using data from large prospective cohorts, with a particular emphasis on health effects of wireless device use.

Before and during his PhD track, he collaborated with the Global Burden of Disease (GBD) project at the Institute for Health Metrics and Evaluation (IHME) at the University of Washington, Seattle, and with the affiliated Italian group of the GBD. His contributions centered on research on GBD methodology and analysis of the global impacts of various risk factors, particularly in relation to air pollution exposure in Italy. In March 2024, he was appointed as an external scientific expert at the European Food Safety Authority (EFSA), providing independent scientific advice within the Genetically Modified Organism (GMO) panel.

In May 2024, Eugenio joined the Netherlands Organization for Applied Scientific Research (TNO) in Utrecht as a scientist in environmental epidemiology. He is currently employed in the department of Risk Analysis for Products in Development (RAPID), where

he continues his work on analysing and quantifying the health impacts of environmental exposures in the Dutch population.

Eugenio is currently a member of the Italian Society of Medical Statistics and Clinical Epidemiology (SISMEC). Since 2020, he has also been actively involved with the Netherlands Society for Statistics and Operations Research (VVSOR).



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