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Development of hypertension after long-term exposure to static magnetic fields among workers from a magnetic resonance imaging device manufacturing facility

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A R T I C L E I N F O

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A B S T R A C T

Objective: To assess the association between long-term exposure to static magnetic fields (SMF) in a magnetic resonance imaging (MRI)-manufacturing environment and hypertension.

Methods: In an occupational cohort of male workers (n = 538) of an MRI-manufacturing facility, the first and last available blood pressure measurements from the facility's medical surveillance scheme were associated with modeled cumulative exposure to SMF. Exposure modeling was based on linkage of individual job histories from the facility's personnel records with a facility specific historical job exposure matrix. Hypertension was defined as a systolic pressure of above 140 mm Hg and/or a diastolic blood pressure above 90 mm Hg. Logistic regression models were used to associate cumulative SMF exposure to hypertension while adjusting for age, body mass index and blood pressure at time of first blood pressure measurement. Stratified analysis by exposure duration was performed similarly.

Results: High cumulative exposure to SMF (≥ 7.4 K Tesla minutes) was positively associated with development of hypertension (Odds Ratio [OR] 2.32, 95% confidence interval [CI] 1.27 – 4.25, $P = 0.006$). Stratified analysis showed a stronger association for those with high cumulative SMF exposure within a period up to 10 years (OR 3.96, 95% CI 1.62 – 9.69, $P = 0.003$), but no significant association was found for (high) cumulative exposure accumulated in a period of 10 or more years. Our findings suggest SMF exposure intensity to be more important than exposure duration for the risk of developing hypertension.

Conclusions: Our data revealed that exposure to high levels of MRI-related SMF during MRI-manufacturing might be associated with developing hypertension.

1. Introduction

Magnetic Resonance Imaging (MRI) is a rapidly developing diagnostic technology with a clear trend to higher field strength scanners and increased application (Capstick et al., 2008; McRobbie, 2012). Occupational exposure to MRI scanners has been associated with self-reported health complaints and workers working with the strongest systems (1.5 and 3 T) tend to report more symptoms (Wilen and de Vocht, 2011). This underlines the importance of the assessment of health risks associated with exposure to MRI-related electromagnetic fields (EMF), including static magnetic fields (SMF). Temporary acute symptoms such as changes in postural sway (van Nierop et al., 2013), changes in visual and visuomotor performance (van Nierop et al., 2012), and neurocognitive effects (de Vocht et al., 2007a, 2006a, 2007b; de Vocht, 2007) have been associated with short-term exposure to MRI-related SMF and time-varying magnetic fields (TvMF), among workers in MRI-production, MRI technicians and clinicians in healthcare, and healthy volunteers. Hardly any data are available on health effects from long-term occupational exposure to SMF (Feychting, 2005; de Vocht et al., 2012). Available epidemiological evidence of (short and long-term) SMF exposure and long-term health effects are predominantly inconclusive due to, e.g. crude exposure assessment and small study sizes (Feychting, 2005). The need for more scientific studies, including epidemiological studies, in this area has been stressed by, among others, the World Health Organisation (van Deventer et al., 2005), the Health Council of the Netherlands (2006) and The Scientific Committee for New and Emerging Health Risk (SCENIHR) (Ahlbom et al., 2008; SCENIHR, 2015). The latter stated that at present there is a lack of adequate data (e.g human observational studies) for a proper risk assessment of occupational exposure to SMF. These institutions

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have emphasized the need for cohort studies focusing on personnel dealing with equipment that generates strong static magnetic flux densities. This is what we set out to do.

The largest groups of SMF-exposed workers (in the Netherlands) are found in clinical and research settings where MRI techniques are being applied (Schaap et al., 2013). Technicians/engineers developing and producing MRI systems, on the other hand, are presumed to have been longer, more frequently and higher exposed (Gowland, 2005), since they generally spend more time near and inside MRI scanners (of various stages of production), which are factors considered to be major determinants of exposure to SMF (Bongers et al., 2013; Fuentes et al., 2008; de Vocht et al., 2009). As part of their work, some of them will probably also have volunteered for image acquisition during the development and manufacturing of MRI scanners. Such MR-volunteer scans result not only in exposure to SMF, but also in exposure to motion induced TvMF, to pulsed time gradient magnetic fields (GMF) and radiofrequency fields (RF). The latter two exposure types are present during active scanning procedures together with exposure to acoustic noise (Bongers et al., 2017). Human and animal studies on cardiovascular effects of acute MRI-related EMF exposure have either shown no effect or indicated an effect within safety limits (Hartwig et al., 2009). Both no change in systolic and diastolic blood pressure (Sert et al., 2010) as well as a slight increase in systolic blood pressure (Chakeres and de Vocht, 2005) in humans with acute exposure have been reported. A hemodynamic compensatory mechanism to counteract the magnetohydrodynamic slowing of the blood flow has been hypothesized as a cause of the observed increase of systolic blood pressure. In addition, generation of free radicals after exposure to SMF has been suggested as a source of oxidative stress, which may lead to hypertension. The underlying mechanisms of exposure to SMF resulting in free radical generation is unclear (Okano, 2008).

The effects of long-term exposure to MRI-related EMF exposure on cardiovascular health is unknown (Hartwig et al., 2009). Here we study long-term occupational exposure to SMF and the development of hypertension in an occupational cohort of male workers of an MRI development and manufacturing facility.

2. Methods

2.1. Study approach and population

For this retrospective cohort study, both exposed and non-exposed current and former workers of a medical imaging device manufacturing facility in the Netherlands were selected using historical company records on employment and occupational health examinations. The base cohort was defined as all workers who had been employed at the manufacturing facility, for at least one year (365 days) between 1984 and 2010, in one or both of the business units Magnetic Resonance (MR) and X-Ray. Workers from the latter business unit were included as a reference group as workers from both business units were assumed to be similar in socioeconomic background and educational level. Workers who during their employment acted as MR-volunteers and had volunteered to undergo an MR-volunteer scan were also included in the base cohort. These groups were not mutually exclusive; part of the eligible workers had worked in both business units, and MR-volunteers worked in these two or other business units of the manufacturing facility.

Historical medical records from the manufacturing facility's health surveillance scheme were analyzed to assess whether occupational long-term exposure to SMF and/or undergoing MR-volunteer scans is associated with development of hypertension. Workers with at least two complete blood pressure measurement records were selected from the base cohort for this purpose. See Fig. 1 for a flow chart of the analytical sample selection process.

2.2. Data from occupational health examinations

Data from the first and last available blood pressure measurements from the following three types of occupational health examinations (see Table 1) were used for the analyses:

1) MR-related periodic occupational health examinations for certain workers of business unit MR (described below) and for workers who underwent MR-volunteer-scans.
2) Entry and exit occupational health examinations for workers of business unit X-ray, mandatory until 2006 to all those who were directly involved in the development or manufacturing of medical imaging devices using ionizing radiation.
3) Periodic occupational health examinations for workers aged 50 and up, offered on a voluntary basis every 2–4 years to all workers of the manufacturing facility aged 50 or older.

The purpose of the MR-related periodic occupational health examinations was to offer auditory testing to MRI-related acoustic noise exposed workers and to precautionary monitor the health status of SMF exposed workers. Hence, from the onset of MRI production in 1984, the manufacturing facility has provided MR-related examinations for its workers working in the vicinity of MRI systems, who were *a priori* considered to be exposed to acoustic noise and/or SMF, and for MR-volunteers. For this purpose, the manufacturing facility categorized workers working at business unit MR in three groups, based on their job title: The assumed highest exposed group was on average more than 4 h a week exposed to SMF; the lowest exposed group was less than 4 h a week exposed, but worked irregularly in the vicinity of an MRI system; and the non-exposed group that did not receive MR-related examinations.

Workers categorized as high and low exposed received an MR-related examination upon start and termination of holding an 'exposed job' at business unit MR. In addition to MR-related examinations upon start and termination, high exposed workers also received an examination every two years until the mid 90's and every three years from then onwards. MR-volunteers received MR-related examinations similar to high exposed workers; upon start of volunteering, every 2–3 years, and/or after undergoing 40 MR-volunteer scans. During an MR-related examination and before each MR-volunteer scan, MR-volunteers were screened for factors contraindicative of MRI safety, such as ferromagnetic implants, claustrophobia or discomfort during a previous MR-volunteer scan, which could exclude MR-volunteers from (temporarily) participating in the MR-volunteer program. At personal discretion of the practicing occupational physician, MR-volunteers could also be excluded from the MR-volunteer program based on results of the examination (e.g. impaired hearing or high blood pressure).

All health examinations were performed by trained occupational physicians or nurses of an external Occupational Health Service commissioned by the manufacturing facility. Aside from systolic and diastolic blood pressure measurements, we used the height and weight measurements from the examinations.

From the mid 90's data from the health examinations were entered directly into an electronic database. The paper medical records from between 1970 until the mid 90's were manually entered into the digital database between 2009 and 2010 for the purpose of our study. To account for human error during data entry, all data in the digital database were screened for anomalous values. Records with possible entry errors (< 1%) were manually compared with the original paper records and corrected when necessary.

2.3. Systolic and diastolic pressure measurements and hypertension definition

Systolic and diastolic blood pressure was measured with a manual sphygmomanometer. During data-entry, the majority of analog

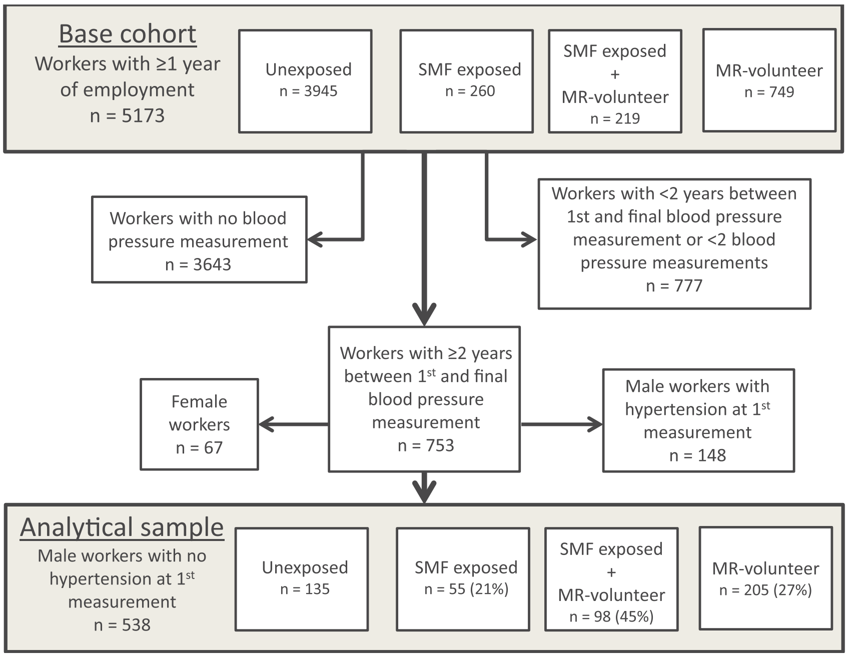

Fig. 1. Flow chart of the analytical sample selection process from a cohort of workers of a medical imaging device development and manufacturing facility: from those with at least 1 year of employment up to and including 2010 (n = 5173), who (had) worked at business units MR and/or X-ray or received at least 1 MR-volunteer scan, the male workers with at least 2 years between the first and final blood pressure measurements with no hypertension at first measurement (n = 538) were selected for the first model analysis. Of this analytical sample, 75 had missing BMI data and were excluded from the second model analyses. From the analytical sample (n = 538), 181 had additional self-reported questionnaire data available on confounders of which 148 with complete BMI data were included in subgroup analyses.

Table 1
Types of occupation health examinations, recipients, schedule and health data collected during each examination type.

Periodical Occupational Health Examination type	Intended for	Occurring	Health data collected
MR-related examination	Low exposed MR workers (less than 4 h a week exposed, but would work irregularly in the vicinity of an MRI system)	Upon entry and exit of business unit MR.	- audiometry testing[a] - blood cell count - cardiac rhythm (ECG, heart rate) - systolic and diastolic blood pressure[a] - height and weight[a]
	High exposed MR workers (on average more than 4 h a week exposed to MRI-related EMF)	Upon entry and exit of business unit MR and every 2 years until mid '90s and every 3 years from then onwards.	
	MR-volunteers	Every 2–3 years, and after undergoing 40 MR-volunteer scans.	
X-ray examination	X-ray workers	Upon entry and exit of business unit X-ray.	- blood cell count - cardiac rhythm (ECG, heart rate) - systolic and diastolic blood pressure[a] - height and weight[a]
Voluntary age-related examination	Workers aged ≥50	Every 2–4 years	- audiometry testing[a] - blood cell count - cardiac rhythm (ECG, heart rate) - systolic and diastolic blood pressure[a] - height and weight[a] - lung function

[a] Records were sufficiently comprehensive for sound analyses.

measurements were routinely, but not always, rounded up or down in increments of 5. To avoid misclassification of non-hypertensive cases as hypertensive ones due to this rounding routine, we defined hypertension as a systolic pressure above 140 mm Hg and/or a diastolic blood pressure above 90 mm Hg, even though the WHO definition is a blood pressure equal to or above these cut offs (World Health Organisation, 2015). Development of hypertension for an individual was defined as hypertension at their final exam in individuals who showed no hypertension at their first exam.

2.4. Analytical sample of the cohort

Out of 5713 workers in the base cohort with an employment duration of ≥ 1 year, a total of 826 workers (686 male and 67 female) had two or more complete records with systolic and diastolic blood pressure measurements with at least two years between the first and the final record. A minimum of two years between measurements was chosen *a priori* to allow for follow-up time between cumulative exposure and development of hypertension, and because MR-related medical examinations took place at 2–3-year intervals. Females were excluded from further analyses due to their small number (n = 67 of which 6 were non-SMF exposed). Of 148 out of 686 male workers with two or more complete blood pressure records with ≥ 2 years between measurements, their first measurement record indicated they already had hypertension, and hence were excluded from the analysis. This prevalence rate of 22% is within the range reported for Dutch males in the general population (Schelleman et al., 2004; Agyemang et al., 2015). The resulting analytical population consisted of 538 male workers (see Fig. 1).

2.5. Occupational SMF exposure during MRI development and production

Occupational SMF exposure was estimated for MR workers using a facility specific historical SMF job exposure matrix (SMF-JEM) developed for this purpose (Bongers et al., 2013), because of paucity of (historical) personal exposure measurements. Historical company records from the salary administration documented employment and job mobility of workers between 1954 and 2010 within the manufacturing facility. These records were, when available, supplemented with self-reported job histories from a questionnaire when specific information on job title was missing (n = 27) (Bongers et al., 2015). Long-term cumulative occupational exposure to SMF was estimated by linking job history data (job title per year based on the company's records) to the SMF-JEM with SMF exposure levels per job title per year between 1984 and 2010. Cumulative SMF exposure, expressed in Tesla minutes (T-min), was calculated as the sum of SMF exposure for each year between 1984 and 2010 over the period from the year of the first blood pressure measurement up to and including the year of final measurement.

The manufacturing facility used a more inclusive definition of exposed worker in the business unit MR to determine eligibility for the MR-examination program than the JEM's definition of an SMF exposed worker. Therefore 43 MR workers who received at least 2 MR-examinations were not considered occupationally SMF exposed when applying the SMF-JEM to their work histories.

2.6. MR-volunteer scan exposure

EMF exposure from a scan procedure as an MR-volunteer was regarded as a different type of EMF exposure than occupational exposure to SMF (the latter is assumed to also serve as a proxy for exposure to low-frequency TvMF from movement through the static magnetic stray field around a scanner (Bongers et al., 2013)). An MR-volunteer will move through the SMF during positioning in and upon leaving the bore, but will remain stationary for the duration of the scan procedure. We included MR volunteer status in our analyses to account for additional exposure to radiofrequency fields (RF) and switched gradient fields (SGF) emitted during a scan procedure in the study population and because of it being a potential source for selection bias (volunteers had to meet certain health standards).

A company protocol for the MR-volunteer program required that each voluntary scan procedure from 1984 onward was recorded, including for each volunteer the date of the scan procedure, MRI scanner type and strength, and scan duration for each procedure. The facility provided all records from 1984 until the end of 2010, without identifying information. The majority of scan procedures was completed with an MRI system with a magnet of 1.5 T (T) or less and lasted on average between 55 and 65 min. Information on magnet strength was missing for 8.4% of data entries and no data was available on the strength of the RF and gradient systems, the driving factors behind two sources of EMF exposure for MR volunteers (Capstick et al., 2008; McRobbie, 2012). Based on this information, cumulative number of scans was considered a crude, but acceptable proxy for MR-volunteer EMF exposure (TvMF, RF, and SGF). 65% (n = 350) of the studied population had undergone MRI scans as a volunteer. The volunteers were from the business unit MR (n = 218), the business unit X-ray (n = 85) or other business units (n = 47). Of the volunteers (n = 98) had also been occupationally exposed to SMF outside the volunteer program.

2.7. Potential confounder data (BMI, smoking behavior and alcohol consumption)

Body Mass Index (BMI) was calculated by weight (kg) divided by (height (m))$^{-2}$. Height and weight were recorded during most, but not all health examinations. This resulted in several missing records on BMI in the study population of 538 workers (n = 179 (33%) at first examination and n = 75 (14%) at final examination). Main analyses were therefore adjusted for BMI at final examination and workers with missing data on BMI at final examination were excluded. In a sensitivity analysis with 320 workers with complete BMI data adjustment for BMI at first examination and for BMI at last examination were compared.

Data on smoking behavior and alcohol consumption were collected in 2010 and 2011 through a questionnaire among current and former workers of the manufacturing facility, and were available for 148 (27%) workers of the analytical sample. See "Bongers et al. (2015)" for a detailed description of the questionnaire. A smoker was defined as a person who reported having smoked more than 100 cigarettes (approximately 5 packages) in their lifetime. An average number of cigarettes smoked per day or week was reported over 10-year age periods (age ≤ 19, 20–29, 30–39, 40–49, 50–59, and ≥ 60) and an average number of pipes smoked per day or week over all years of age was reported. One pipe was considered equivalent to 2.5 cigarettes (Wood et al., 2005). Reported starting and (when applicable) quitting age of smoking, were combined with reported smoking rates to estimate (cumulative) pack-years ((number of cigarettes smoked per day/20) × number of years smoked) up until the end of the year of final blood pressure measurement. The estimated pack-year value did not account for periods of smoking cessation as no information was available on duration and time period of cessation.

Alcohol consumption was assessed for workers who reported consuming alcoholic beverages at least once a month. 53 workers with BMI at final examination and questionnaire data reported no alcohol consumption up to the final examination. Data were collected on starting and (if applicable) quitting age and on how many units of alcoholic beverages consumed on average per week at specific age periods (≤ 19, 20–39, 40–59, and ≥ 60). See "Bongers et al. (2015)" for a detailed description of alcohol unit count of different beverages. A count of 1 to ≤ 14 units/ week was scored as low alcohol consumption and a count of > 14 units/week was scored as high alcohol consumption. The cumulative number of years of self-reported low and high alcohol consumption was estimated up until the end of the year of final blood pressure measurement. Years of low and high alcohol consumption were set to 0 for workers reporting no alcohol consumption.

2.8. Statistical analyses

One-sample binominal test and one-sample median test were applied to compare binominal and continuous data on characteristics, respectively, between the unexposed reference group and different exposure subgroups (occupational SMF exposure and MR-volunteer scan exposure, which were not mutually exclusive).

Two logistic regression models were used to assess the associations between cumulative exposure to SMF and development of blood pressure (systolic > 140 mm Hg and/or diastolic > 90 mm HG at final examination, yes versus no). The first model included as cofactors EMF exposure from MR-volunteer scans, age at final examination (continuous), and systolic and diastolic blood pressure at first examination (continuous, mmHg). The second model additionally adjusted for BMI during the final blood pressure examination (above 25 versus 25 and below). The second model was also stratified by duration of the period between first and final health examinations (2 up to 10 years, and 10 or more years) to evaluate the effect of duration of exposure period and exposure intensity. Workers with 10 or more years between first and final examination had more time to accumulate SMF exposure and will have been exposed at a lower intensity than workers with less than 10 years between examinations, but with a similar cumulative exposure level.

In addition, a subgroup analysis was done, to explore effects of lifestyle factors, i.e. a third model with besides BMI additional adjustment for smoking and alcohol consumption within the subpopulation for which questionnaire data was available.

Cumulative exposure to SMF was divided in three categories: no exposure (0 T-min), low exposure (1-7413 T-min), and high exposure

Table 2
Characteristics of analytical population (n = 538) with at least two complete blood pressure measurements. Results are shown for male workers with ≥ 2 years between first and final available complete record of systolic and diastolic blood pressure and who had no hypertension at first measurement record.

	Non-exposed	Occupational SMF exposure only	Occupational SMF exposure + MR-volunteer-related exposure	MR-volunteer-related exposure only
N°	135	55	98	250
Age at first measurement, median [range]	31 [16–58]	31 [17–54]	31 [20–54]	36.5 [16–58]**
Age at last measurement, median [range]	42 [26–63]	41 [29–58]	43 [29–69]	47 [23–65]**
Time between first and last measurement (years), median [range]	5.9 [2.0–31.4]	6.1 [2.7–32.5]*	10.7 [2.9–36.2]**	7.4 [2.0–34.9]**
Cumulative modeled SMF exposure between years of first and last measurements (T-min), median [range]	–	9583.5 [7.7–83,725.0]	2906.4 [8.8–148,888.8]◊◊	–
Cumulative number of MR-volunteer scans between years of first and last measurements, median [range]	–	–	19 [1–110]	23 [1–177]††
Hypertension at final measurement, N (%)	33 (24%)	18 (33%)	18 (18%)	48 (19%)
Data on BMI, N (%)	128 (95%)	52 (95%)	86 (88%)*	194 (78%)**
BMI ≥25 at final measurement, N (% of population with BMI data)	66 (52%)	25 (48%)	39 (45%)	104 (54%)
Workers with additional questionnaire data on smoking and alcohol consumption (%)	5 (4%)	17 (31%)**	45 (45%)**	114 (46%)**
Ever smoker, N (% of subpopulation)	2 (40%)	7 (41%)	16 (36%)	51 (45%)
Pack years among ever smokers up to year of final examination, median [range]	5.7 [4.8–6.7]	11.2 [4.6–34.3]*	9.7 [0.1–51.6]*	8.5 [0.3–37.0]*
Low alcohol consumption up to year of final examination, N (% of subpopulation)	3 (60%)	13 (76%)	38 (84%)**	93 (48%)**
Years of low alcohol consumption among low alcohol consumers up to year of final examination, median [range]	30 [10–34]	22 [2–40]	21.5 [4–40]**	23 [1–48]**
High alcohol consumption up to year of final examination, N (% of subpopulation)	2 (40%)	7 (41%)	14 (31%)	35 (31%)
Years of high alcohol consumption among high alcohol consumers up to year of final examination, median [range]	28 [2–36]	16 [4–41]	18 [2–41]	20 [2–41]

* P < 0.05, one-sample median test or two sided binominal test between indicated exposure sub-category (Occupational SMF exposure only, Occupational SMF exposure + MR-volunteer-related exposure, or MR-volunteer-related exposure only) versus the non-exposed reference group.

** P < 0.001, one-sample median test or two sided binominal test between indicated exposure sub-category (Occupational SMF exposure only, Occupational SMF exposure + MR-volunteer-related exposure, or MR-volunteer-related exposure only) versus the non-exposed reference group.

◊◊ P < 0.001, one-sample median test between exposure sub-categories occupational SMF exposure only and occupation SMF exposure + volunteer-related exposure.

†† P < 0.001, one-sample median test between exposure sub-categories MR-volunteer related exposure only versus occupational SMF exposure + MR-volunteer related exposure.

(> 7413 T-min), where the cut-off point for SMF exposed was based on median occupational SMF exposure of exposed workers. 139 SMF exposed workers with data on BMI were included in the analyses that stratified between 2 and 10 years and ≥ 10 years between first and final examination. 38 (55%) of the 69 low exposed workers and 32 (46%) of the 70 high exposed workers had less than 10 years between examinations.

Exposure to MR-volunteer scan-related EMF was divided into three categories: no exposure (0 scans), low exposure (1–21 scans) and high exposure (> 21 scans), where the cut-off point for MR-volunteer scan exposure was based on median number of MR-volunteer scans within the population of MR-volunteers.

In the analysis within the subpopulation of exposed workers with data on smoking and alcohol consumption, the cut off for cumulative exposure to SMF was based on the median cumulative exposure to SMF exposure: no exposure (0 T-min), low exposure (1-3467 T-min), and high exposure (> 3467 T-min). Similarly the cut points were the 33th and 66th percentiles of number of MR-volunteer scans among MR-volunteers. This resulted in the following groups: no to low exposure (0–20 scans), medium exposure (21–40 scans), and high exposure (> 40 scans). The reference group included non-SMF exposed workers who had never received an MR-volunteer scan and non-SMF exposed MR-volunteers with up to 20 scans, due to low number (n = 3) of non-SMF exposed non-MR-volunteers workers with data on smoking and alcohol consumption.

The median pack-years among smokers was 9.29 years and the median number of years of low use of alcohol among workers reporting alcohol consumption was 24 years. Smoking was categorized as follows: no (never smoker), low (>0-9.29 pack-years), high (>9.29 pack-years and alcohol consumption was categorized as: low (0-24 years of low use of alcohol, medium (>24 years of low use of alcohol, but no high use of alcohol), and high (≥1 year of high use of alcohol).

Analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA.) and a P-value of < 0.05 was considered statistically significant.

3. Results

Table 2 shows the characteristics of the study population and the subpopulation for which questionnaire data on alcohol and smoking was available. The SMF exposed workers are of comparable age as the non-SMF exposed workers at their first and final blood pressure measurement and have similar hypertension rates at final measurement. A larger portion of the MR-volunteers (SMF exposed and non-exposed) had missing data on BMI than non-MR-volunteers. Within the SMF non-exposed population, MR-volunteers were significantly, although slightly, older than workers without MR-volunteer exposure. MR-volunteers with additional occupational SMF exposure had 1) a lower median number of MR-volunteer scan than MR-volunteers without occupational SMF exposure, 2) more time between first and final measurements than workers from the SMF non-exposed reference group, and 3) lower median cumulative exposure to SMF than non-volunteer workers exposed to SMF. Despite these small differences, the non-exposed reference group was considered a suitable reference population.

High cumulative occupational SMF exposure (≥ 7413T-min) was positively associated with developing hypertension (Odds Ratio (OR) 2.38, (95% CI 1.33 – 4.28)) and this OR stayed virtually the same when adjusted for BMI (2.32 (95% CI 1.27 – 4.25)). No association was found with low cumulative SMF exposure (Table 3). Both a low and high cumulative number of MR-volunteer scans were negatively associated with developing hypertension (OR 0.54 (95% CI 0.30 – 0.97) and OR 0.62 (95% CI 0.35 – 1.09), respectively) compared to not having undergone volunteer scans (Table 3).

A sensitivity analysis among workers with data on BMI at first and last examination (n = 320) showed that only a BMI of ≥ 25 at last examination was associated with risk of developing hypertension which justifies the decision for our main analyses.

The subgroup analysis with additional adjustment for smoking and alcohol consumption, showed a rather stronger than weaker association between high occupational SMF exposure and hypertension (OR 8.35 (95% CI 2.22 – 31.38)) (Table 4).

When stratified for duration of the time between first and final examination, with BMI adjustment, a stronger association was found between high SMF exposure and developing hypertension for workers with less than 10 years between examinations. The negative association between MR-volunteer exposure and developing hypertension remained similar within this stratified group. No association between either (high) SMF exposure or volunteer exposure and developing hypertension was found for workers with exposure accumulated over 10 or more years (Table 3). While the median and maximum cumulative SMF exposure (9896 and 148,888 T-min) was higher in the ≥ 10 years than in the up to 10 years between examinations sub-population (5351 and 90,381 T-min), the maximum and median of the average SMF exposure (cumulative SMF (T-min)/time between examinations (years)) was lower in the former sub-population (458 and 1219 T-min/y) than in the latter sub-population (737 and 13,950 T-min/y), indicating a lower intensity of SMF exposure in the former group.

4. Discussion

We found an association between high occupational SMF exposure and the risk of developing hypertension that does not appear to be caused by potential confounding lifestyle factors (BMI, alcohol and smoking). The association is strongest in the population of workers with high cumulative exposure accumulated in less than 10 years between first and final blood pressure measurement, suggesting that intensity of exposure may also play a role. The median first year of examination was 2002 for the sub-population with up to 10 years between examinations, compared to 1989 for the sub-population with ≥ 10 years between examinations. While the latter group of workers had more time to accumulate a high cumulative SMF exposure level, which is reflected in higher cumulative exposure levels, they worked during the early days of MRI production and before the introduction of MRI systems with stronger magnets. For instance 3 T systems were only taken into production in 2001 at the manufacturing facility (Bongers et al., 2013). Previously higher exposure intensity has been linked to a higher rate of self-reported acute health complaints after acute exposure (Wilen and de Vocht, 2011). Here we note that intensity of long-term exposure may result in chronic health effect as well.

Our study is unique as it studied prospectively collected data on blood pressure that could be associated with estimates of long-term occupational exposure to SMF during MRI development and production, and EMF exposure during voluntary MRI-scans among workers from an MRI-systems manufacturing facility. While effects of acute MRI-related EMF exposure have been studied in the manufacturing environments as well as in clinical settings (Feychting, 2005; Bongers et al., 2015; de Vocht et al., 2006b; Schaap et al., 2014) and among human volunteers (van Nierop et al., 2013; de Vocht et al., 2007b), few studies have been published on health effects of long-term occupational exposure to SMF. A study with the same occupational population from the manufacturing facility indicated an increased risk of accidents associated with high occupational SMF exposure (Bongers et al., 2015).

We have explored potential confounding by alcohol consumption and smoking, known risk factors of developing hypertension (World Health Organisation, 2013). We could do this in a subpopulation for which we had additional questionnaire data. In this sub-population high SMF exposure was still found to be associated with an increased risk of developing hypertension.

While the workers from the business unit X-Ray were considered a suitable reference group, no data was available on their potential exposure to ionizing radiation. Epidemiological evidence is still inconclusive for low to medium occupational exposure to ionizing radiation and cardiovascular health effects (Little and Lipshultz, 2016; Baselet

Table 3
Multivariate logistic regression of the association between cumulative occupational SMF exposure (T-min) and MR-volunteer scan exposure (Number of scans) between first and final available blood pressure measurement (with ≥ 2 years between first and final measurement) and developing hypertension for male workers with no hypertension at first measurement, adjusted for age at final measurement, systolic and diastolic blood pressure at first measurement (n = 538), and additionally adjusted for BMI at final measurement for all workers with ≥ 2 years between first and final measurement (n = 460), workers with ≥ 2 and < 10 years between first and final measurement (n = 276) and workers with ≥ 10 years between first and final measurement (n = 184).

	First model		Second model		Second model, stratified by exposure duration			
	taking account of MR-volunteer scan exposure and adjusted for age and blood pressure at first examination (n= 538)[a]		additionally adjusted for BMI (n= 463)[a,b]		< 10 years between first and final measurement (n= 277)[a,b]		≥ 10 years between first and final measurement(n= 186)[a,b]	
	Odds Ratio	**95% Confidence intervals**	**Odds Ratio**	**95% Confidence intervals**	**Odds Ratio**	**95% Confidence intervals**	**Odds Ratio**	**95% Confidence intervals**
Unexposed	1		1		1		1	
Occupational SMF exposure Low (1- <7413 T-min)	0.83	0.41 – 1.67	0.71	0.33 – 1.51	1.28	0.48 – 3.40	0.33	0.09 – 1.25
Occupational SMF exposure High (≥7413 T-min)	**2.38**	**1.33 – 4.28** *(P = .004)*	**2.32**	**1.27 – 4.25** *(P = .006)*	**3.96**	**1.62 – 9.69** *(P = .003)*	1.16	0.49 – 2.76
MR-volunteer scan exposure Low (1–21 scans)	**0.49**	**0.28 – 0.84** *(P = .01)*	**0.54**	**0.30 – 0.97** *(P = .03)*	**0.42**	**0.19 – 0.96** *(P = .04)*	0.89	0.36 – 2.17
MR-volunteer scan exposure High (>21 scans)	**0.57**	**0.33 – 096** *(P = .04)*	0.62	0.35 – 1.09	0.80	0.35 – 1.84	0.58	0.26 – 1.31
Age at final measurement (years)	**1.05**	**1.02 – 1.08** *(P = .0003)*	**1.04**	**1.01 – 1.07** *(P = .005)*	1.03	0.99 – 1.07	1.04	0.99 – 1.09
Systolic pressure at first measurement (mmHg)	**1.07**	**1.04 – 1.10** *(P < .0001)*	**1.06**	**1.03 – 1.09** *(P < .0001)*	1.09	**1.05 – 1.13** *(P < 0.0001)*	1.02	0.98 –1.07
Diastolic pressure at first measurement (mmHg)	1.02	0.99 – 1.05	1.02	0.98 – 1.05	1.01	0.96 – 1.06	1.04	0.99 –1.09
BMI at final measurement ≥ 25			**1.77**	**1.09 – 2.84** *(P = .02)*	1.37	0.70 – 2.65	**2.63**	**1.21 – 5.71** *(P = .01)*

[a] Male workers with no hypertension at first measurement adjusted for age at final measurement, and systolic and diastolic blood pressure at first measurement.
[b] Additionally adjusted for BMI at final measurement; which was not available for 538–463 = 75 subjects.

Table 4
Multivariate logistic regression of the association between cumulative occupational SMF exposure (T-min) and MR-volunteer scan exposure (Number of scans) between first and final blood pressure measurement and developing hypertension for workers without hypertension at first measurement (n = 148) corrected for blood pressure at first measurement, age and BMI, and additionally adjusted for alcohol consumption and smoking.

	Third model in subgroup			
	(n = 148)[a]		additionally adjusted for alcohol consumption and smoking (n = 148)[a,b]	
	Odds ratio	**95% Confidence Limits**	**Odds ratio**	**95% Confidence Limits**
Reference group (non-exposed with no to low MR-volunteer-related exposure)[c]	1		1	
Occupational SMF exposure Low (1-<3467 T-min)	0.58	0.14 – 2.37	0.59	0.14 – 2.46
Occupational SMF exposure High (≥3467 T-min)	**6.39**	**1.86 – 21.94** *(P = .003)*	**8.35**	**2.22 – 31.38** *(P = .002)*
MR-volunteer scan exposure Medium (21–40 scans)	0.87	0.25 – 3.00	0.88	0.25 – 3.12
MR-volunteer scan exposure High (> 40 scans)	1.31	0.41 – 4.13	1.23	0.40 – 4.16
Age at final measurement (years)	**1.07**	**1.00 – 1.12** *(P = 0.02)*	**1.10**	**1.02 – 1.18** *(P = .001)*
Systolic blood pressure at first measurement (mm Hg)	**1.10**	**1.04 – 1.17** *(P = .001)*	**1.11**	**1.04 – 1.18** *(P = .0008)*
Diastolic blood pressure at first measurement (mm Hg)	1.02	0.95 – 1.09	1.01	0.99 – 1.08
BMI at final measurement ≥ 25	0.78	0.29 – 2.07	0.85	0.30 – 2.40
Low alcohol consumption			0.58	0.15 – 2.18
High alcohol consumption			0.70	0.19 – 2.65
Smoking Low			0.75	0.20 – 2.80
Smoking High			0.39	0.10 – 1.55

[a] Male workers with no hypertension at first measurement adjusted for age at final measurement, systolic and diastolic blood pressure at first measurement, and BMI at final measurement.
[b] Additionally adjusted for alcohol consumption and smoking.
[c] Note that this is a different reference group as the one presented in Table 3 due to low number of non-SMF non-MR-volunteers.

et al., 2016) and it was not possible to correct our analyses for potential ionizing radiation exposure, but exposure levels were expected to be within permitted occupational levels.

A limitation of this study is the lack of noise measurement data at business units MR as MRI systems are known to produce high levels of acoustic noise (McJury and Shellock, 2000) or at other workplaces within the manufacturing facility. Long-term (occupational) noise exposure is found to be related to an increased risk of developing hypertension (Passchier-Vermeer and Passchier, 2000). While no historical measurement data was available on work-related noise exposure at the manufacturing facility (at business unit MR or elsewhere), general occupational noise exposure not directly related to MRI specific procedures (i.e. general noise emitted during manufacturing) was considered similar for all business units. No corrections were made for general occupational noise exposure. In addition, MR-workers were instructed to minimize MRI-related (noise) exposure by leaving the MRI room when an MRI scan procedure was in progress. MRI-related occupational acoustic noise exposure was therefore considered low.

MR-volunteer-related noise exposure was managed with mandatory use of hearing protection devices. MR-volunteer-related acoustic noise exposure was associated with a small increase of hearing loss (Bongers et al., 2017) which implies the potential of an additional noise exposure for MR-volunteers despite the use of hearing protection. MR-volunteer-related acoustic noise exposure may constitute an additional risk factor for developing hypertension, but given that we saw a protective effect for being a volunteer on the chance of developing hypertension this effect must have been minimal.

Our findings suggest a much stronger effect from "healthy volunteer" selection within the study population. Workers with contra-indicative conditions were barred from becoming or remaining an MR-volunteer, thus resulting in a selection of potentially healthier MR-volunteers with lower probability of developing hypertension despite MR-volunteer-related acoustic noise exposure.

Workers considered as high SMF exposed received periodical health examinations in addition to entry and exit examinations and the effects of receiving more health examinations than the reference group is unknown. There was no data available from the health surveillance scheme regarding hypertension diagnosis or use of medication to manage high blood pressure among the studied workers and it is unknown whether periodical examinations led to medication use or change in life style related to hypertension management. To survey the prevalence of these factors in the study population, health questionnaire data (Bongers et al., 2015) from a subsample the study population (n = 227) were analyzed. 39 workers (17%) reported hypertension diagnosed by a doctor of which 16 (7%) reported a diagnosis before their final blood pressure measurement. A group of 29 workers (13%) reported being prescribed medication to manage hypertension, although no data was available on whether medication was taken before their final blood pressure measurement. 7 of the 16 workers with a doctor's diagnosis before final examination were not considered hypertension cases in our study, which may be due to hypertension management. In addition to hypertension management encouraged by a doctor's diagnosis, the repeated medical examinations among workers with high SMF exposure and MR-volunteers may have led to increased health awareness among this group compared to the reference group of workers who received two medical examinations. Both factors could have potentially led to an underestimation of hypertension risk through a healthy worker effect.

The data available for this study originate from the manufacturing facility's (precautionary) health surveillance program and were originally not collected for research purposes. Despite this the quality of the blood pressure data was sound enough to demonstrate an association between known contributing factors (i.e. age and BMI) and an increased risk of developing hypertension.

We found an association between high cumulative occupational exposure to MRI-related SMF and developing hypertension among workers of an MRI manufacturing facility, with a fourfold risk for the highest exposed workers compared to non-exposed workers. Exposure intensity appeared to have a stronger influence than exposure duration with a risk that varies between 2.3 and 4.0 depending on the model assumptions for the highest exposed workers compared to non-exposed workers.

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Contributorship and conflict of interest

Author SB was the main contributor to data collection, analyses, and drafting the manuscript. All authors have contributed equally to the design of the study and critical revision of the manuscript. All authors have read the manuscript, agree the work is ready for submission to a journal, and accept responsibility for the manuscript's contents. All authors declare no (potential) conflict of interest.

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