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ORIGINAL PAPER

Longitudinal bidirectional associations between internalizing mental disorders and cardiometabolic disorders in the general adult population

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Abstract

Purpose This prospective population-based study investigated whether having any internalizing mental disorder (INT) was associated with the presence and onset of any cardiometabolic disorder (CM) at 3-year follow-up; and vice versa. Furthermore, we examined whether observed associations differed when using longer time intervals of respectively 6 and 9 years.

Methods Data were used from the four waves (baseline and 3-, 6- and 9-year follow-up) of the Netherlands Mental Health Survey and Incidence Study-2, a prospective study of a representative cohort of adults. At each wave, the presence and first onset of INT (i.e. any mood or anxiety disorder) were assessed with the Composite International Diagnostic Interview 3.0; the presence and onset of CM (i.e. hypertension, diabetes, heart disease, and stroke) were based on self-report. Multilevel logistic autoregressive models were controlled for previous-wave INT and CM, respectively, and sociodemographic, clinical, and lifestyle covariates.

Results Having any INT predicted both the presence (OR 1.28, $p=0.029$) and the onset (OR 1.46, $p=0.003$) of any CM at the next wave (3-year intervals). Having any CM was not significantly related to the presence of any INT at 3-year follow-up, while its association with the first onset of any INT reached borderline significance (OR 1.64, $p=0.06$), but only when examining 6-year intervals.

Conclusions Our findings indicate that INTs increase the risk of both the presence and the onset of CMs in the short term, while CMs may increase the likelihood of the first onset of INTs in the longer term. Further research is needed to better understand the mechanisms underlying the observed associations.

Keywords Internalizing mental disorders · Cardiometabolic disorders · Adult general population · Prospective cohort study

Introduction

Internalizing mental disorders (INTs), i.e. mood and anxiety disorders, and cardiometabolic disorders (CMs), e.g. hypertension, diabetes, heart disease, and stroke, rank among the leading causes of years lived with disability (YLDs) [1, 2] and disability-adjusted life years (DALYs) [3, 4] worldwide. Research has shown that INTs and CMs frequently coexist and that this comorbidity is generally associated with worse health outcomes, lower quality of life and functioning, and greater health care utilization [5–11]. This stresses the relevance of clarifying the temporal relationship between INTs and CMs; are INTs associated with the onset and course of CMs or vice versa, or both? Such knowledge is useful for strategies to prevent the onset and poor outcomes of these types of mental and physical disorders.

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Whether INTs increase the risk of CMs has been extensively studied, but with a focus on specific conditions. Meta-analyses of longitudinal studies have found evidence that both depressive and anxiety disorders increase the risk of developing hypertension, diabetes, heart disease, and stroke [9, 12–22]. Noteworthy, some meta-analyses [13–15, 20, 21] included not only longitudinal studies of participants who were free of the CM of interest at baseline (incidence studies) but also considered studies including participants who had the CM of interest at baseline (prevalence studies). It is relevant to distinguish between these two types of studies because they have different implications. Incidence studies provide evidence as to whether or not INTs play a role in the onset of CMs, while prevalence studies generate evidence as to whether or not INTs negatively impact the course of pre-existing CMs.

The reverse relationship, i.e. whether CMs increase the risk of INTs, has been the subject of less longitudinal research. These studies also concentrated on specific CM-INT combinations. Two meta-analyses demonstrated that having diabetes increases the risk of developing depressive disorder [23, 24]. Noteworthy, some of the studies included in these meta-analyses did not exclude participants with a history of depressive disorder at baseline. The possibility of reverse causation therefore cannot be excluded in these studies, i.e., a previous depressive episode that contributed to the onset of diabetes. Furthermore, the meta-analyses did not consider prevalence studies, i.e., studies including participants with an existing depressive disorder at baseline, which provide evidence on whether diabetes influences the course of depressive disorder or not. Two other meta-analyses indicated that there exist too few studies to draw conclusions about the associations between diabetes and incident anxiety disorders [13] and between hypertension and incident depressive disorder [25]. These meta-analyses also did not include prevalence studies.

The focus of previous longitudinal research on specific INT-CM combinations, with particular attention to depressive disorder, can be considered an important limitation. The high rates of co-occurrence of individual CMs [10, 26, 27] and co-occurrence of individual INTs [28, 29], point to shared underlying mechanisms. Indeed, CMs are considered as expressions of a limited set of underlying intertwined disease processes (e.g. glycemic dysregulation and atherosclerosis) of which the manifestations in specific diseases are relatively secondary from an etiological perspective [30, 31]. In a similar vein, internalizing psychopathology is conceptualized as representing the underlying core psychopathological processes that result in specific disorders such as depressive and anxiety disorders [32, 33]. If the goal is to better understand the ways in which these physical and mental processes interact it is thus preferable to measure these disease dimensions as comprehensively as possible. Therefore, one should adopt a broad perspective and study the bidirectional longitudinal association between any (combination of) INT(s) and any (combination of) CM(s), rather than focus on a specific INT-CM combination. As far as we know, longitudinal studies with such a broad approach do not yet exist.

Prior longitudinal research is also limited in other respects. Most studies have examined the direction of INT-CM associations from only one direction. Preferably, the potential bidirectional longitudinal relationship between INTs and CMs is examined using the same study sample and dataset to allow a direct comparison between the strengths of the observed bidirectional associations [34]. Another limitation is that most prior individual studies have not examined a possible influence of follow-up duration. Yet, meta-analyses indicated that the strengths of longitudinal INT-CM associations differ depending on the length of follow-up [15, 17, 20, 22, 24].

Aims of the study

The present study aims to expand current knowledge about the bidirectional longitudinal association between INTs and CMs by addressing the limitations of previous research described above. Data were used from the four waves (baseline and 3-, 6- and 9-year follow-up) of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), a longitudinal study of a representative cohort of adults. Specifically, we aimed to determine whether having an INT at a certain wave predicted the presence and onset of any CM at the next wave (3 years later) and vice versa. Furthermore, we examined whether the observed associations differed when using longer time intervals of respectively 6 and 9 years.

Methods

Study design

NEMESIS-2 is a psychiatric epidemiological cohort study of the Dutch general population aged 18–64 at baseline [35]. It is based on a multistage, stratified random sampling of households, with one respondent randomly selected in each household. The face-to-face interviews were laptop computer-assisted. In the first wave (T_0; November 2007-July 2009), 6646 persons were interviewed (response rate: 65.1%; average duration: 95 min). This sample was nationally representative, although younger subjects were somewhat underrepresented [35].

All T_0 respondents were approached for follow-up (T_1), three years after T_0. Of these, 5303 persons could be interviewed again (response rate: 80.4%, with those deceased excluded; average duration: 84 min). All T_1 respondents

were approached for a second follow-up (T_2), 3 years after T_1; 4618 persons were re-interviewed (response rate: 87.8%; average duration: 83 min). At third follow-up (T_3), 3 years after T_2, 4007 persons could be re-interviewed (response rate: 87.7%; average duration: 101 min). Attrition between T_0 and T_3 was not significantly associated with any INT in the past 12 months at T_0, nor with any CM in the past 12 months at T_0, after controlling for sociodemographics.

Measures

INTs

DSM-IV diagnoses were made using the Composite International Diagnostic Interview (CIDI) version 3.0, a fully structured lay-administered diagnostic interview. This instrument was developed for use in the World Mental Health Survey Initiative [36].

The INTs considered in this study included mood disorders (major depression, dysthymia, and bipolar disorder) and anxiety disorders (panic disorder, agoraphobia without panic disorder, social phobia, specific phobia, and generalized anxiety disorder). Clinical calibration studies in various countries [37] found that the CIDI 3.0 assesses these disorders with generally good validity in comparison to blinded clinical reappraisal interviews.

At T_0, INTs during lifetime and the past 12 months were assessed; at the follow-up waves, INTs during the past three years and the past 12 months were assessed.

CMs

CMs were assessed by means of self-report, using a standard questionnaire assessing the presence of 16 common chronic somatic diseases. This questionnaire is used in various large scale cohort studies [35, 38] and the annual Health Survey of Statistics Netherlands (CBS) among a large representative sample of the Dutch population. The following CMs were considered: hypertension, diabetes, severe cardiac disease or myocardial infarction, and stroke (cerebral infarction or haemorrhage) or its consequences. These disorders were only regarded as present if the respondent reported that they were treated or monitored by a medical doctor in the previous 12 months. In general, comparisons between self-reports of chronic physical disorders and medical records show moderate to good concordance [39, 40].

At all waves, CMs in the past 12 months were assessed. At T_0, data on CMs were missing for 140 participants as they were administered a shortened interview [35]. These participants could be included in the analysis as long as they had observations on the dependent variables at one or more of the follow-up waves, provided the predictor variables were also observed for that participant for that time point.

Potential confounders

Based on previous research [41], a selection was made of variables related to both INTs and CMs.

Sociodemographic covariates were: gender, age, educational level (4 categories), and partner status.

Clinical and lifestyle covariates were: somatic comorbidity (i.e. presence of ≥ 1 of 12 other chronic somatic disorders, such as asthma, chronic obstructive pulmonary disease, stomach or intestinal ulcers, chronic back pain, arthrosis, migraine, and cancer, which are treated or monitored by a medical doctor in the previous 12 months, as assessed with the aforementioned questionnaire), psychotropic medication (especially use of antidepressants or benzodiazepines in the previous 12 months prescribed by a physician), BMI (body mass index, kg/m^2), smoking (in the past month), physical activity (assessed using the International Physical Activity Questionnaire [42] and defined as 5 or more days per week of moderate-intensity activity at least 30 min a day, which corresponds to the Dutch norm for sufficient physical activity) and alcohol use (4 categories). Alcohol use was based on two CIDI-questions regarding frequency of use and number of drinks on typical drinking days in the past year. The total number of alcoholic drinks per week (frequency by amount) was categorized into: none (0 drinks weekly), mild (< 8 drinks weekly), moderate (8–14 drinks weekly for women and 8–21 drinks weekly for men), and high average (> 14 drinks weekly for women and > 21 drinks weekly for men) drinking levels, according to international guidelines [43, 44].

Statistical analysis

Multilevel logistic autoregressive models were used to examine the bidirectional prospective INT-CM associations. Multilevel models take into account the nested character of the data with observations at the four waves nested in individuals, and can adequately deal with missing observations by using all available data (under the 'missing at random' assumption, which was tested and seemed reasonable in our data).

The first set of analyses explored whether having any INT predicted the presence of any CM during the next 3 years of follow-up and vice versa. In the model for CM, the presence of any CM at T_1, T_2, and T_3 (CM_t) was predicted from the presence of any INT at the previous wave (INT_{t-1}), adjusting for the presence of CM at the previous wave (CM_{t-1}). In the model for INT, the presence of any INT at T_1, T_2, and T_3 (INT_t) was predicted from the presence of any CM at the previous wave (CM_{t-1}), adjusting for the presence of INT at the previous wave (INT_{t-1}). In these models, the associations between INT_{t-1} and CM_t (or CM_{t-1} and INT_t, respectively) are called cross-lagged effects. These were our

main interest. The associations between CM_{t-1} and CM_t (or INT_{t-1} and INT_t, respectively) are referred to as autoregressive effects. We used any INT in the past 12 months at T_0 and any INT in the past 3 years at T_1, T_2 and T_3, to cover the entire interwave interval. We used any CM in the past 12 months at all waves, since CM was only assessed with respect to the preceding year. A two-step approach was conducted to adjust for potential confounders. In Model 1, we only adjusted for sociodemographic variables (gender, education, age_{t-1}, partner $status_{t-1}$), while in Model 2 clinical and lifestyle variables (somatic $comorbidity_{t-1}$, psychotropic $medication_{t-1}$, BMI_{t-1}, $alcohol_{t-1}$, $smoking_{t-1}$, physical $activity_{t-1}$) were also considered. All covariates were dichotomous (0/1), except education, BMI, and alcohol use (ordinal variables with 4 levels) and age (continuous). We used lagged values of all time-varying confounders, to preclude reverse causality.

To test whether cross-lagged effects at different waves were similar, we tested interactions between INT_{t-1} and wave number (or CM_{t-1} and wave number, respectively). Neither of these interactions was significant, justifying the pooling of these effects into a single 3-year cross-lagged effect per model. To test cross-lagged effects at longer follow-up, we compared whether the addition of lag-2 (6-year intervals) and lag-3 (9-year intervals) cross-lagged effects significantly contributed to the model using Likelihood ratio tests, additionally controlling for lag-2 and lag-3 autoregressive effects.

A limitation of the above analyses is that the severity of INTs and CMs is not considered, while severity factors (e.g. severity of symptoms, degree of functional impairment) may influence the association between INTs and CMs [9, 15, 18, 23]. Therefore, as sensitivity analyses, the analyses were repeated using ordinal versions of the predictor and outcome variables (i.e. number of CMs and INTs, respectively). The number of conditions can be considered a basic indicator of underlying severity.

The second set of analyses examined whether having any INT predicted the onset of any CM at 3-year and longer-term follow-up periods, and vice versa. In the model for CM, the participants were selected who reported no CM in the twelve months prior to T_0. For those who developed any CM at T_1, T_2, or T_3, observations at later waves were removed from the dataset, to ensure that all cases at later waves were incident cases. In the model for INT, we selected the participants without a lifetime history of INT at T_0, and removed all observations at later waves for those who developed any INT at T_1, T_2, or T_3. Thus, in these models predicting the onset of any CM and any INT at follow-up, respectively, all observations of participants who developed a CM or an INT at an earlier time point were removed, to ensure that all cases were onset cases. Using datasets with only incident cases, predictors for autoregressive effects could be removed from the models. Apart from that, the same analysis steps were performed as in the first set of analyses.

Models were estimated in Stata using the melogit command. Robust standard errors were used for the regression coefficients. Models with different random effects and covariance structures were tested, and the most optimal model was selected using the Bayesian Information Criterion (BIC). Linearity assumptions of ordinal covariates were tested by checking whether models with dummy specifications for the different levels of these covariates had a better model fit than models in which these covariates were entered as continuous variables. The latter model specification showed the best fit according to the BIC for all these three covariates. Multicollinearity was checked by inspecting VIF values, which were all below recommended levels of 5. The model fit of the final models was evaluated by inspection of plots of predicted versus observed probabilities. Marginal predicted probabilities were calculated using Stata's margins command.

Results

Study population characteristics

Table 1 shows the characteristics of the baseline sample. The mean age of the respondents was 44.3 years, and more than half (55.3%) were female.

Table 2 illustrates that the prevalence of any INT in the previous 12 months was somewhat higher at baseline (T_0) than at the three follow-up waves, whereas the prevalence of any CM in the past 12 months increased over time.

Any INT as a predictor of the presence of any CM at follow-up, and vice versa

Short-term follow-up results (3-year intervals)

Table 3 (upper panel) shows that, when adjusting for sociodemographics (Model 1), previous-wave INT predicted the presence of any CM at the next wave (3-year interval) (INT_{t-1}: OR 1.33; 95% CI 1.08–1.63; $p = 0.006$). This effect remained significant after adjustment for clinical and lifestyle variables (Model 2, OR 1.28; 95% CI 1.03–1.60; $p = 0.029$), and implies that the odds of having any CM at follow-up was 28% higher for participants having any INT at the previous wave compared to participants without INTs. In terms of marginal predicted probabilities, this means that having any INT increased the probability of having any CM at the next wave from 17.5% to 19.3% (marginal on observed values of all other covariates). As shown in Table 3 (lower panel), the reverse relationship was also significant in Model 1, i.e. previous-wave CM was associated with the presence of any INT at the next wave (CM_{t-1}: OR 1.22; 95%

Table 1 Baseline characteristics of the study sample ($N=6646$)

	Mean/%	SD/*n*
Age (mean, SD)	44.3	12.5
Gender (% female, *n*)	55.3	3672
Education (%, *n*)		
Primary, basic vocational	5.0	332
Lower secondary	27.5	1826
Higher secondary	32.3	2145
Higher professional, university	35.3	2343
Living without a partner (%, *n*)	32.2	2140
Comorbid somatic conditions (%, *n*)	24.0	1563
Psychotropic medication (%, *n*)	6.4	415
BMI (%, *n*)		
Underweight	1.8	117
Normal	52.9	3501
Overweight	33.3	2203
Obese	12.0	795
Alcohol use (%, *n*)		
None	18.1	1202
Mild	56.2	3736
Moderate	19.3	1282
High average	6.4	425
Smoking (%, *n*)	30.6	1988
Physical activity (% reaching Dutch norm, *n*)	41.8	2692

Some observations are missing for some of the baseline variables

BMI body mass index

CI 1.03–1.45; $p=0.021$). However, when adjusting additionally for clinical and lifestyle variables (Model 2), this cross-lagged association was substantially reduced and not significant anymore.

Autoregressive effects were (very) strong in both models, implying that the presence of any CM and any INT was rather stable across the 3-year follow-up intervals. Unsurprisingly, this was especially true for any CM. In the full model (Model 2) predicting the presence of any CM at follow-up, a higher educational level and a higher level of physical activity significantly lowered the risk of any CM, while higher age, having no partner and higher BMI exerted the opposite effect. In the full model predicting the presence of any INT at follow-up, female gender, having no partner, lower age, the presence of somatic comorbidity, using a psychotropic medication, smoking, and lower level of physical activity significantly increased the risk of INT.

Longer-term follow-up results (6- and 9-year intervals)

Six-year interval effects were studied by running the models of Table 3 again, but now including lag-2 cross-lagged and autoregressive effects. The total number of observations in these models was reduced to 8563 ($n=4609$). The addition of the lag-2 cross-lagged effects did not significantly improve the model fit of Model 1 (INT_{t-2} in the model for the presence of any CM: $chi^2(1)=3.36$, $p=0.07$); CM_{t-2} in the model for the presence of any INT: $chi^2(1)=0.97$, $p=0.32$). We therefore did not proceed with Model 2. Similarly, adding lag-3 cross-lagged effects (9-year follow-up interval), while adjusting for lag-3 autoregressive effects, did not improve the fit of Model 1 ($n=3954$, the total number of observations 3954; INT_{t-3} in the model for the presence of any CM: $chi^2(1)=1.03$, $p=0.31$); CM_{t-3} in the model for the presence of any INT: $chi^2(1)=0.90$, $p=0.34$). Thus, including longer-term cross-lagged effects (i.e. 6- and 9-year intervals) did not improve the models examining 3-years interval effects.

Table 2 The prevalence of any internalizing mental disorder (INT) (upper part of the table) and any cardiometabolic disorder (CM) (lower part of the table) at the four measurement waves

Any INT	T_0 $N=6646$	T_1 $N=5303$	T_2 $N=4618$	T_3 $N=4007$
Lifetime prevalence, *n* (%)	2087 (31.4%)			
Prevalence in the past 12 months, *n* (%)	911 (13.7%)	497 (9.4%)	440 (9.5%)	379 (9.5%)
Prevalence in the past 3 years, *n* (%)	–	655 (12.4%)	559 (12.1%)	513 (12.8%)
Age at lifetime onset, median (IQR)	17 (9–30)			
Age of onset during follow-up waves, median (IQR)		43 (34–53)	47 (39–55)	50 (39–57)
Any CM	T_0 $N=6506$	T_1 $N=5303$	T_2 $N=4618$	T_3 $N=4007$
Prevalence in the past 12 months, *n* (%)	822 (12.6%)	896 (16.9%)	885 (19.2%)	803 (20.0%)
Age of onset, median (IQR)	46 (37–54)	49 (40–56)	50 (40–58)	50 (42–59)

IQR interquartile range

Table 3 Multilevel logistic autoregressive models for the prediction of the presence of any cardiometabolic disorder (CM) (upper part of the table) and the presence of any internalizing disorder (INT) (lower part of the table) from previous-wave INT and CM (3-years intervals)

	Model 1			Model 2		
	OR	95% CI	*p*	OR	95% CI	*p*
Any CM_t						
Any INT_{t-1}	1.33	1.08–1.63	.006	1.28	1.03–1.60	.029
Any CM_{t-1}	51.8	39.2–68.6	< .001	47.8	35.3–64.8	< .001
Female gender	0.80	0.70–0.91	.001	0.88	0.76–1.01	.070
Education	0.81	0.76–0.87	< .001	0.91	0.85–0.98	.018
No $partner_{t-1}$	1.16	1.00–1.34	.048	1.24	1.07–1.45	.005
Age_{t-1}	1.06	1.05–1.07	< .001	1.06	1.05–1.07	< .001
Somatic $comorbidity_{t-1}$				1.11	0.95–1.29	.184
Psychotropic $medication_{t-1}$				0.99	0.74–1.31	.924
BMI_{t-1}				1.99	1.80–2.19	< .001
Alcohol use_{t-1}				1.01	0.92–1.10	.824
$Smoking_{t-1}$				1.12	0.96–1.32	.150
Physical $activity_{t-1}$[a]				0.81	0.71–0.93	.003
Any INT_t						
Any CM_{t-1}	1.22	1.03–1.45	.021	1.10	0.92–1.31	.290
Any INT_{t-1}	4.50	3.69–5.49	< .001	3.43	2.78–4.22	< .001
Female gender	1.58	1.39–1.79	< .001	1.56	1.37–1.78	< .001
Education	0.87	0.81–0.93	< .001	0.94	0.88–1.01	.092
No $partner_{t-1}$	1.42	1.25–1.60	< .001	1.31	1.15–1.48	< .001
Age_{t-1}	0.98	0.98–0.98	< .001	0.98	0.97–0.98	< .001
Somatic $comorbidity_{t-1}$				1.51	1.32–1.72	< .001
Psychotropic $medication_{t-1}$				2.97	2.42–3.64	< .001
BMI_{t-1}				1.09	0.99–1.18	.054
Alcohol use_{t-1}				1.00	0.92–1.09	.941
$Smoking_{t-1}$				1.40	1.23–1.60	< .001
Physical $activity_{t-1}$[a]				0.87	0.77–0.98	.027

$N = 5279$; total number of observations = 13,842. Random effects only significant for autoregressive effects

BMI body mass index

[a]Reaching Dutch norm

Sensitivity analyses

A limitation of the above analyses is that the severity of INTs and CMs was not taken into account. Therefore, as sensitivity analyses, we reran the short-term models (3-year intervals), now using the number of INTs and CMs as the predictor and outcome variables (see Supplemental Table 1). Results were comparable to those of the original models using the dichotomized variants of the outcome measures (see Supplemental Table 2).

Any INT as a predictor of the onset of any CM at follow-up, and vice versa

Short-term follow-up results (3-year intervals)

At baseline (T_0), 5684 participants had no CM in the past 12 months (87.4%). At 3-year follow-up (T_1), 364 participants developed any CM (7.8% of the 4642 remaining participants at T_1), while at 6-year follow-up (T_2) there were 206 incident cases (5.5% of the 3721 remaining participants at T_2), and at 9-year follow-up (T_3) there were 146 incident cases (4.8% of the 3046 remaining participants at T_3).

Table 4 (upper panel) shows that previous-wave INT significantly predicted the onset of any CM at the next wave (3-year interval), both when only controlling for sociodemographics (Model 1; OR 1.60; 95% CI 1.28–1.99; $p < 0.001$) and when adjusting additionally for clinical and lifestyle variables (Model 2; OR 1.46; 95% CI 1.14–1.87; $p = 0.003$). The effects of covariates were comparable to those in the model predicting the presence of any CM. The OR of 1.46 for the effect of any INT_{t-1} in predicting the onset of any CM in Model 2 implies that the odds for the development of any CM at follow-up was 46% higher for participants having any INT at the previous wave compared to participants without INTs. In terms of marginal predicted probabilities, this means that having any INT increases the probability

Table 4 Multilevel logistic autoregressive models for the prediction of the onset of any cardiometabolic disorder (CM) (upper part of the table) and the first onset of any internalizing disorder (CM) (lower part of the table) from previous-wave INT and CM (3-years intervals)

	Model 1			Model 2		
	OR	95% CI	*p*	OR	95% CI	*p*
Onset of any CM						
Any INT_{t-1}	1.60	1.28–1.99	< .001	1.46	1.14–1.87	.003
Female gender	0.75	0.64–0.87	< .001	0.84	0.71–0.99	.038
Education	0.77	0.71–0.84	< .001	0.90	0.82–0.98	.019
No $partner_{t-1}$	1.11	0.93–1.31	.247	1.19	0.99–1.43	.061
Age_{t-1}	1.06	1.05–1.07	< .001	1.06	1.05–1.07	< .001
Somatic $comorbidity_{t-1}$				1.14	0.95–1.36	.158
Psychotropic $medication_{t-1}$				1.07	0.77–1.48	.678
BMI_{t-1}				2.10	1.87–2.34	< .001
Alcohol use_{t-1}				1.03	0.92–1.15	.615
$Smoking_{t-1}$				1.16	0.97–1.40	.108
Physical $activity_{t-1}$[a]				0.84	0.71–0.99	.037
First onset of any INT						
Any CM_{t-1}	1.30	0.98–1.71	.064	1.17	0.87–1.57	.293
Female gender	1.53	1.28–1.84	< .001	1.53	1.26–1.87	< .001
Education	0.85	0.77–0.95	.003	0.92	0.83–1.03	.145
No $partner_{t-1}$	1.25	1.02–1.52	.029	1.17	0.96–1.44	.126
Age_{t-1}	0.97	0.96–0.98	< .001	0.97	0.96–0.98	< .001
Somatic $comorbidity_{t-1}$				1.49	1.21–1.84	< .001
Psychotropic $medication_{t-1}$				3.11	1.93–5.01	< .001
BMI_{t-1}				1.04	0.91–1.19	.572
Alcohol use_{t-1}				0.99	0.86–1.13	.860
$Smoking_{t-1}$				1.47	1.19–1.80	< .001
Physical $activity_{t-1}$[a]				0.85	0.70–1.02	.080

$N = 4642$, total number of observations = 11,409 (model CM); random effects not significant; $N = 3596$, total number of observations = 9042 (model INT)

BMI body mass index

[a]Reaching Dutch norm

of developing any CM at the next wave from 5.8% to 8.1% (marginal on observed values of the other covariates).

At baseline (T_0), 4559 participants had no lifetime history of INT (68.6%). At 3-year follow-up (T_1), 227 participants experienced the first onset of any INT (6.3% of the 3618 remaining participants at T_1), while at 6-year follow-up (T_2) there were 161 first-onset cases (5.4% of the 2999 remaining participants at T_2), and at 9-year follow-up (T_3) there were 123 first-onset cases (5.0% of the 2482 remaining participants at T_3).

Table 4 (lower panel) shows that, when only taking into account sociodemographics (Model 1), the association of previous-wave CM with the first onset of any INT at the next wave trended towards statistical significance (OR 1.30; 95% CI 0.98–1.71; $p = 0.064$). When adjusting additionally for clinical and lifestyle variables (Model 2), the OR was reduced to 1.17 and no longer significant (95% CI 0.87–1.57; $p = 0.293$). Again, the effects of covariates were rather similar to those in the model for predicting the presence of any INT.

Longer-term follow-up results (6- and 9-year intervals)

Six-year interval effects were tested by re-running the models of Table 4, but now including lag-2 cross-lagged effects. The total number of observations in these models was reduced to 6767 ($n = 3721$) in the model predicting the onset of any CM, and 5446 ($n = 2993$) in the model predicting the first onset of any INT. The addition of the lag-2 cross-lagged effect of any INT in the model for the onset of any CM did not significantly improve the model ($chi^2(1) = 2.14$, $p = 0.14$) (Model 1). However, the lag-2 cross-lagged effect of any CM significantly improved model fit in the model for the first onset of any INT ($chi^2(1) = 4.32$, $p = 0.04$) (Model 1). The size of this cross-lagged effect was OR 1.68 (95% CI 1.04–2.71; $p = 0.04$). The lag-1 cross-lagged effect (3-year intervals) was not significant in this model (CM_{t-1}: OR 0.96; 95% CI 0.60–1.55; $p = 0.88$). When controlling additionally for clinical and lifestyle covariates (Model 2), the cross-lagged effect of CM_{t-2} was slightly reduced to 1.64 and trended towards statistical significance (95% CI 0.99–2.72;

$p = 0.06$; $n = 2984$, the total number of observations = 5417). Adding lag-3 cross-lagged effects (9-year intervals) also did not improve the models (INT_{t-3} in the model for the onset of any CM: $chi^2(1) = 1.27$, $p = 0.26$; $n = 3046$, the total number of observations 3046); CM_{t-3} in the model for the first onset of any INT: $chi^2(1) = 2.23$, $p = 0.14$; $n = 2453$, the total number of observations 2453). To summarize, these results indicate that a relatively short follow-up duration (~ 3 years) is sufficient to show an effect of any INT on the onset of any CM, while a relatively long follow-up duration (~ 6 years) is needed to detect an effect of any CM on the first onset of any INT.

Discussion

The current study found that, after adjusting for sociodemographics, clinical and lifestyle covariates, having any INT was associated with both the presence and the onset of any CM at short-term (3-year) follow-up intervals. No indications were found for stronger effects when examining the two longer-term (i.e. 6- and 9-year) follow-up intervals. These findings suggest that the psychopathology underlying INT or its consequences contributes both to a less favourable course of any pre-existing CM as well as to the onset of any CM, and that these negative impacts occur after a relatively short time period. Our findings are consistent with previous research that has focused on specific INT-CM combinations. Meta-analyses have indicated that both depressive and anxiety disorders might be associated with a poorer course of heart disease and diabetes [45–48]. Other meta-analyses have shown that both depressive and anxiety disorders are predictors of the onset of respective hypertension, diabetes, heart disease, and stroke [9, 12–22]. Some of these latter meta-analyses examined whether the pooled estimates were influenced by the length of follow-up of included studies. Most meta-analyses found higher risk estimates in studies with shorter follow-up duration [15, 19, 20, 22], while other meta-analyses observed the reverse [17], or no influence of follow-up duration [9, 12, 14, 16]. This inconsistency may be partly due to the large variation between meta-analyses in the follow-up periods that were compared with each other (e.g. definition of a 'shorter' follow-up duration ranged from ≤ 4.2 to < 15 years).

When looking at our findings concerning the inverse relationship (i.e. CM predicting INT), a different picture emerged. After controlling for all covariates, no indications were found that having any CM was associated with the presence of any INT at follow-up. However, having any CM predicted the first onset of any INT, though only at longer-term (6-year) follow-up intervals: adjusting for sociodemographics (Model 1) the odds ratio for this effect was 1.68 (significant), decreasing only minimally to 1.64 (borderline significant) when adjusting additionally for the other covariates (Model 2). Taken together, these findings can be interpreted as indicating that having any CM has no impact on the course of any co-existing or preceding INT but may be associated with the first onset of any INT in the longer term. Such an interpretation is in line with previous studies among patients admitted for myocardial infarction (MI) that found MI severity to be associated with the first onset of depressive disorder, but not with recurrent or ongoing depressive disorder after the MI [49–52]. To explain this finding, researchers have postulated that first incident depressive disorder after MI is mainly triggered by severe underlying cardiac disease or its consequences in persons with normal vulnerability to depressive disorder (i.e. without a lifetime history of the depressive disorder) [50, 52]. Our findings may suggest that such a mechanism relates to the broad category of any CM: the severity of the disease process underlying CM or its consequences can serve as a trigger for the first onset of any INT in individuals with normal vulnerability to internalizing psychopathology. Furthermore, our findings may suggest that such an effect only occurs after a relatively long period of time (~ 6 years).

The present study expands previous research in various ways. First, the longitudinal relationship between any INT and any CM was examined, rather than investigating specific INT-CM combinations, which represent comparatively less comprehensive measures of the underlying mental and physical processes. Second, the bidirectional INT-CM associations were examined using the same study sample and data set, rather than focusing on the directionality of the association from only one side. Third, we used as many as four waves, which increased power substantially and enabled the examination of different follow-up durations (i.e. 3-, 6- and 9-year intervals) on observed associations. Additional study strengths included the large representative sample of the Dutch adult general population, the use of a standardized diagnostic instrument (CIDI 3.0) to assess the presence and first-ever onset of INT, and the possibility to adjust for a range of potential confounders.

Yet, some limitations merit discussion. First, although the sample was reasonably representative of the Dutch adult population [35], younger adults, adults with an insufficient mastery of Dutch, adults with no permanent residential address, and institutionalized adults, were (somewhat) underrepresented. It is unclear how the underrepresentation of these groups of adults might have affected our findings. Anyhow, the findings cannot simply be generalized to these groups. Second, in our analyses we could not meaningfully take into account the potential influence of ethnicity, as the group of participants of non-western origin was too small (i.e. 5.7% of the baseline sample [35]). Third, the assessment of CMs was based on self-report. Although it has been shown that this method has acceptable validity [39,

40], respondents without CMs may have misreported the presence or onset of CMs. However, such misclassification is not very likely because respondents were asked whether they were treated or monitored by a physician for any reported CM. Conversely, respondents may have underreported CMs that causes no or mild symptoms, such as mild hypertension or early stages of diabetes. Both types of misclassification would likely have attenuated the observed associations. Fourth, the severity of CMs and INTs was only considered crudely in sensitivity analyses by examining the association of the presence of the number of CMs at the previous wave with the presence of the number of INTs at the next wave (3-year interval), and vice versa. The results were similar to those of the main analyses concerning the presence of any CM and any INT. Fifth, since the lifetime history of any CM was not assessed at baseline, the onset of any CM at follow-up measurements could have concerned recurrent (rather than first-onset) disorder in some cases. Therefore it cannot be entirely excluded that the observed association of having any INT with the subsequent onset of any CM may partially reflect reverse causation, i.e. a prior history of any CM that contributed to the onset of any INT at baseline measurement. Sixth, although we adjusted for important baseline sociodemographic, clinical, and lifestyle characteristics, the possibility exists that any observed relationship might partially have resulted from non-measured sources of confounding. Finally, while the odds ratio for the effect of having any CM on the first onset of INT at 6-year follow-up intervals only decreased marginally in Model 2 (adjusting for all covariates) as compared to Model 1 (adjusting for sociodemographics), it was no longer statistically significant in the former full model, but borderline significant ($p = 0.06$). Although this may be due to the fact that some of the covariates in Model 2 may act as mediators of the CM effect, this merits cautious interpretation.

In conclusion, our findings indicate that INTs increase the risk of both the presence and the onset of CMs in the short term, while CMs may increase the likelihood of the first onset of INTs in the longer term. Further long-term longitudinal research, including more detailed measurement of the severity of INTs and CMs, the examination of the effects of the length of follow-up, and careful consideration of potential confounding, mediating, and moderating variables, is needed to confirm our findings and better understand the mechanisms underlying the observed associations. Prior research has suggested a wide range of possible factors to explain bidirectional links between specific INTs and CMs, including biological (e.g. neuroendocrine dysregulation, immunological/inflammation effects, genetic susceptibility), psychological (e.g. negative expectations of future health, low level of perceived self-control), behavioral (e.g. unhealthy lifestyles, sleep disturbance, reduced adherence to treatment regimens), pharmacological (e.g. effects of prescribed medication), and severity (e.g. severity of symptoms, degree of physical or mental impairment, treatment intensity) factors [9, 15, 18, 23]. Furthermore, given that INTs and CMs are leading causes of burden of disease, the findings of the present study have clinical and public health importance. Our findings suggest that healthcare professionals should be alert to the possible onset of any CM in adults with any INT, and vice versa. Moreover, this study points to the importance of appropriate management of any co-existing INT among adults with any CM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval NEMESIS-2 was approved by the Medical Ethics Review Committee for Institutions on Mental Health Care (METIGG). After having been informed about the study aims, respondents provided written informed consent at each wave.

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