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ORIGINAL PAPER

12-year changes in cardiovascular risk factors in people with major depressive or bipolar disorder: a prospective cohort analysis in Germany

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Abstract

Background Major depressive disorder (MDD) and bipolar disorder are associated with certain cardiovascular risk factors (CVRFs), but it is unclear whether they are associated with unfavourable changes of clinically manifest CVRFs over time.
Methods We used baseline and 12-year follow-up ($n = 1887$) data from the German Health Interview and Examination Survey 1998. Multivariable linear regression models assessed associations between lifetime CIDI-diagnosed mood disorders at baseline and continuous risk factor-related outcomes (blood pressure, HbA1c, LDL-C, HDL-C, triglycerides, BMI) at follow-up.
Results We did not find consistent deterioration of CVRFs in persons with compared to persons without MDD. Analyses pointed to severity of mood disorder as an important correlate of long-term changes of comorbid hypertension: while a history of mild MDD was not associated with changes in CVRFs, moderate MDD was associated with lower blood pressure [systolic: $\beta = -7.5$ (CI -13.2; -1.9); diastolic: $\beta = -4.5$ (CI -7.8; -1.3)] and a history of bipolar disorder was associated with higher systolic blood pressure at follow-up ($\beta = 14.6$; CI 4.9–24.4). Further, severe MDD was weakly associated with a higher BMI at follow-up [$\beta = 1.2$ (CI 0.0; 2.4)]. These outcomes were not mediated by use of psychotropic medication and remained statistically significant after adjusting for the use of antihypertensive medication.
Conclusion Since most investigated parameters showed no associations, participants with a lifetime history of MDD in this cohort did not carry a specific risk for a worsening of pre-existing clinically manifest CVRFs. Our findings extend evidence of MDD severity and bipolar disorder as important correlates of long-term changes of arterial hypertension and obesity.

Keywords Major depressive disorder · Bipolar disorder · Epidemiology · Hypertension · Cardiovascular risk factor

Introduction

Mood disorders such as bipolar disorder or major depressive disorder (MDD) are common in Western countries. In Germany, approximately 17% (MDD) and 1% (bipolar disorder) of the population are affected during lifetime [1,

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2]. These disorders are positively associated with higher all-cause mortality [3, 4], among other things pointing to the importance of physical comorbidity. Associations of these disorders with cardiovascular disease are well known (e.g. [5–7]). For example, prospective cohort studies of participants with baseline depressive symptoms reported an association with incident cardiovascular disease [8], individuals with depression are ~ 50% more likely to develop cardiovascular events, which is largely explained by severity of depressive symptoms and behavioural factors [9] and these disorders predispose even early cardiovascular disease in youth [10].

Cardiovascular risk factors (CVRFs) are major causes of cardiovascular disease and represent an important link between mood disorders and cardiovascular disease [11]. In contrast to associations with cardiovascular disease and mortality, the body of evidence regarding the association of different CVRFs with MDD is less consistent: for people with MDD, meta-analyses of cross-sectional studies report a higher comorbidity with CVRFs such as metabolic syndrome, hyperglycaemia and hypertriglyceridemia [12], as well as an increased prevalence of diabetes mellitus type 2 [13]. For people with bipolar disorder, the comorbid prevalence of a metabolic syndrome [14, 15], hypertension [6, 16] and diabetes mellitus [17] is even higher compared to other mood disorders. While a systematic review and meta-analysis of depression in later life and CVRFs reported higher frequencies of key diseases such as diabetes, cardiovascular disease and stroke, here no relations were found with CVRFs such as hypertension, smoking or dyslipidemia [18]. It is unclear whether these disorders are associated with changes of already clinically manifest CVRFs over time, since most of the analysed studies used data comparing incident CVRFs, and not their potential improvement or worsening over time. Considering the immense importance of managing prevalent CVRFs in daily practice of general and internal medicine, this is particularly interesting.

Mood disorders are not a clinically homogenous entity regarding symptom severity, use of available treatments and consecutive impairment of quality of life [19] and there is a growing body of evidence showing that especially severe conditions such as bipolar disorders are associated with a particularly high cardiovascular mortality [20] which is possibly predicted by severity of disease, e.g. manic symptom burden [21]. As recently suggested by prospective analysis of data from the UK, this mortality gap in severe mental illnesses might even be widening in comparison with the general population [22]. On the other hand, so far it is not known whether the severity of a mood disorder is differentially correlated with long-term changes of already clinically manifest CVRFs. Accordingly, we used population-based data from baseline and 12-year follow-up examination of the German National Interview and Examination Study (GHS) to investigate changes of pre-existing arterial hypertension, diabetes mellitus, dyslipidemia or obesity in participants with or without a history of MDD of different severity or bipolar disorder.

Methods

Study sample

We used baseline and 12-year follow-up data from the GHS [1, 23]. GHS (field work 1997–1999) involved 7124 participants (response rate 61.41%) living in Germany aged 18–79. A stratified random sample was drawn from 130 sampling units in 113 communities throughout Germany. The survey included a self-report questionnaire, a computer-assisted personal interview (CAPI), a laboratory assessment and a screening for mental disorders, which served as the first stage of the mental health supplement (GHS-MHS, field work 1997–1999) [23, 24]. In the second stage of the GHS-MHS ,the World Health Organization Composite International Diagnostic Interview (CIDI) [25] was administered to participants from the core survey who were screened positive for a mental disorder and to a random sample of 50% who were screened negative. After exclusion of participants older than 65 years due to unclear validity of the CIDI-interview for this age group, a total of 4181 participants (conditional response rate 87.6%) were fully examined in the survey's mental health supplement [1].

The German Health Interview and Examination Survey for Adults (DEGS1) was conducted between 2008 and 2011. Only DEGS1-participants who had participated in GHS and GHS-MHS were included in our analyses. Panel attrition from GHS-MHS to DEGS1 was 51%. After removing participants with missing values in at least one of the exposures, outcomes or covariates, 1887 participants with complete longitudinal data were available. In this sample, the average time from GHS to DEGS1 was 11.99 years (mean 623.7 weeks; SD 54.2). As depicted in Fig. 1, the resulting sample sizes for prospective analyses were $n = 541$ for participants with prevalent arterial hypertension at baseline, $n = 85$ for participants with diabetes mellitus at baseline, $n = 929$ for participants with dyslipidemia at baseline and $n = 326$ for participants with obesity at baseline.

All participants provided written informed consent. The studies comply with the Declaration of Helsinki and the German Federal Data Protection Act [24, 26].

Measures of mood disorder

Lifetime diagnoses of MDD and bipolar disorder (including bipolar I disorder and bipolar II disorder) were assessed in the GHS-MHS [24] using a computer-assisted version

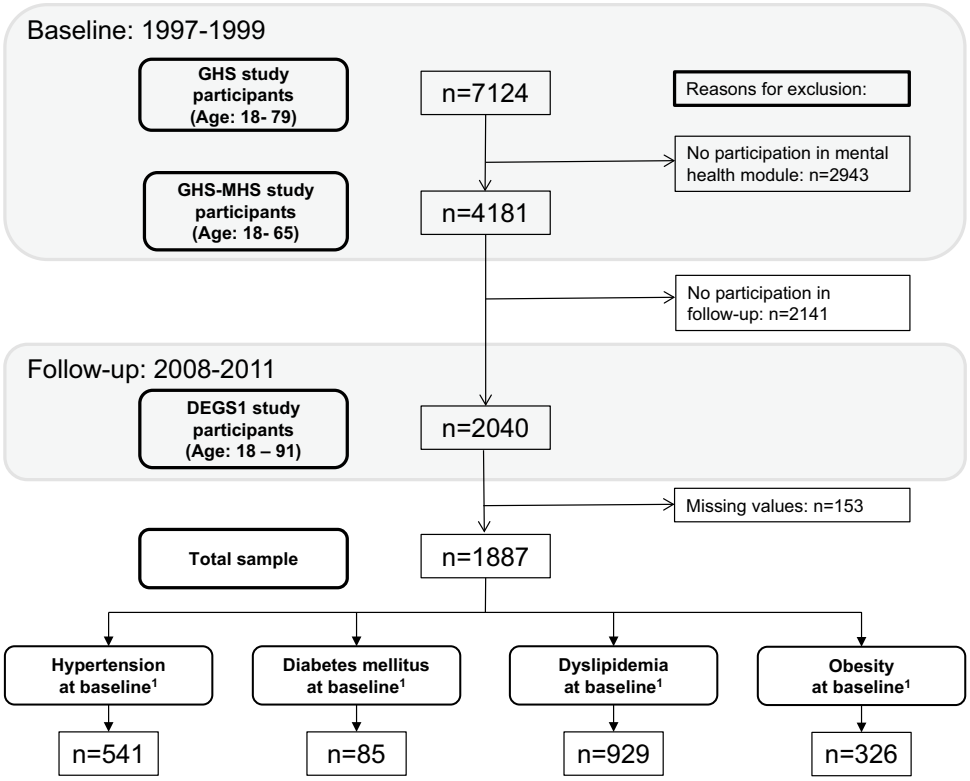

Fig. 1 Flow diagram of study participants for prospective analyses. 1 Due to comorbidity the subsamples for prospective analyses are not clearly separated groups. *GHS* German National Interview and Examination Study, *GHS-MHS* German National Interview and Examination Study mental health supplement, *DEGS1* German Health Interview and Examination Survey for Adults

of the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI) [27]. The CIDI is an internationally established, standardised psychiatric interview allowing the assessment of lifetime diagnoses of different mood disorders using the diagnostic criteria of the DSM-IV [25].

We conducted separate analyses for MDD and bipolar disorder, and grouped the participants diagnosed with MDD by three degrees of symptom severity according to DSM-IV:

- Single episode or recurrent mild MDD
- Single episode or recurrent moderate MDD
- Single episode or recurrent severe MDD with or without psychotic symptoms

For our analysis, we calculated prospective associations for five different predictor categories with the absence of the respective disorder as reference category: (1) lifetime diagnosis of any MDD; (2) lifetime diagnosis of mild MDD; (3) lifetime diagnosis of moderate MDD; (4) lifetime diagnosis of severe MDD; (5) lifetime diagnosis of any bipolar disorder.

For mediation analyses and to substantiate the clinical relevance of this grouping of MDD, we investigated baseline and follow-up frequencies of psychopharmacotherapy. Study participants brought their original drug containers to the survey site at baseline and follow-up examination, where they were scanned and automatically coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System [28]. The following ATC codes were considered as relevant for the treatment of the investigated mood disorders: N05A (Antipsychotics; Incl. Lithium), N06A (Antidepressants).

Definition of subsamples by cardiovascular risk factors

For longitudinal analysis, we defined four subsamples of participants: persons with prevalent arterial hypertension, diabetes mellitus, dyslipidemia or obesity at baseline:

- *Arterial hypertension* was defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [29]: systolic blood pressure $\geq$ 140 mmHg or diastolic blood pressure $\geq$ 90 mmHg or use of antihypertensive medication (ATC codes: C02A, C03C, C03A, C03E, C09BA, C07A, C08CA, C08DA01, C09AA, C09CA, C09B, C09D, C08G) or diagnosis by a physician.
- *Diabetes mellitus* was defined under consideration of the recommendations from the American Diabetes Association [30]: HbA1c $\geq$ 6.5% or non-fasting glucose $\geq$ 11.1 mmol/l or use of antidiabetic medication (ATC codes A10A, A10B) or diagnosis by a physician.
- *Dyslipidemia* was defined based on the guidelines from the National Cholesterol Education Program

Adult Treatment Panel III [31]: LDL-C > 4.1 mmol/l or HDL-C < 1.04 mmol/l (men)/HDL-C < 1.3 mmol/l (women) or TG ≥ 6.2 mmol/l or use of statins or fibric acid derivates (ATC code C10AA, C10AB).

- *Obesity* was defined based on WHO recommendations [32] as a BMI ≥ 30 kg/m^2.

A more detailed description on the survey methods is available in the supplementary material. Subsamples were not mutually exclusive; people with more than one of these diagnoses are considered in each of the relevant subsamples. A detailed description on the number of comorbid CVRFs in each subsample can be found in Supplemental Table 1.

Change of cardiovascular risk factors

Within each of these subsamples, the change of risk factors was operationalized by investigating associations between the examined continuous parameters at follow-up (systolic/diastolic blood pressure, HbA1c, LDL-C, HDL-C, TG, BMI) and a diagnosed history of mood disorder, while controlling for respective baseline measurements.

To investigate whether outcome changes in participants with CVRFs were related to the use of medication, we additionally adjusted our analyses for the use of disease-specific medication (ATC codes above) at baseline and follow-up. As recommended before [33, 34], the continuous measures in the hypertension and dyslipidemia subsamples were adjusted for medication use based on the estimated average effects of the respective medication. As proposed by Cui et al. [35] and Licht et al. [34], a constant value of 10 mmHg (systolic blood pressure) and 5 mmHg (diastolic blood pressure) was added to the blood pressure measurements of individuals with antihypertensive medication. Continuous measures in the dyslipidemia subsample were adjusted for the estimated average effects of statin and fibrate use: statins—LDL-C (+ 1.08 mmol/l) [36], HDL-C (− 0.06 mmol/l) [37], triglycerides (+ 0.2 mmol/l) [37]; fibrates—LDL-C (+ 0.36 mmol/l) [38], HDL-C (− 0.1 mmol/l) [34], triglycerides (+ 0.67 mmol/l) [34]. The adjustment for an average treatment effect of antidiabetic medication has to be considered a very rough approximation, since the average treatment effect of antidiabetic drugs highly depends on the used agent, individual insulin sensitivity and the HbA1c level when treatment is initiated [39]. Information on these respective HbA1c measures was not available for our study. In the absence of a validated method to adjust for the use of antidiabetic medication in our study, we report no respective analysis for HbA1c levels.

Further, we evaluated change of CVRF-specific medication by calculating relative risks for an intensified treatment regimen at follow-up. Since data on doses were not available, we defined an intensified treatment by the prescribed agents: hypertension—no use of antihypertensive medication at baseline and use of antihypertensive medication at follow-up or more antihypertensive agents at follow-up than at baseline; diabetes—no use of antidiabetic medication at baseline and use of antidiabetic medication at follow-up or one antidiabetic agent at baseline and a combination of insulin and another blood glucose-lowering agent at follow-up or no insulin at baseline and insulin at follow-up; dyslipidemia—no use of statin or fibrate at baseline and use of statin or fibrate at follow-up or fibrate or statin at baseline and a combination of both at follow-up.

Assessments of co-variables

A disjunctive cause criterion [40] was used to select covariates to adjust for confounding. Education was grouped as < 10, 10, > 10 years of schooling. Smoking status (never, ex-smoker, or current smoker) and alcohol consumption (in grams per day) were obtained in a standardised computer-assisted personal interview [23].

Statistical analyses

Baseline characteristics are presented for the total sample, participants with hypertension, diabetes, dyslipidemia and obesity using weighted means for continuous and percentages for categorical variables. Calculated percentages do not necessarily add up to 100% due to rounding. Multiple linear regression models were used to assess associations of mood disorders with continuous outcomes (blood pressure, HbA1c, LDL-C, HDL-C, TG, BMI) at follow-up. The assumption of normally distributed errors was checked visually. Further, we investigated relations of antihypertensive medication use with blood pressure changes in participants with prevalent arterial hypertension at baseline. Because ignoring or excluding participants on disease-specific medication or adjusting for medication using a covariate in a regression analysis can bias estimates in an ordinary linear regression [33], we adjusted our models at baseline and/or follow-up as described above. Additionally, relations of mood disorders with an intensified disease treatment at follow-up were examined using relative risks (RR) and 95% confidence intervals (CI) from Poisson regression with robust standard errors [41]. One regression model was run for each exposure–outcome combination. We tested for multiplicative interaction with age using Wald tests. We tested the missing-completely-at-random (MCAR) assumption underlying the complete case analysis using a binary logistic regression for participation at the follow-up examination with baseline values of the outcomes, mood disorders/severity, age, sex, education, alcohol consumption, and smoking. In case the resulting regression estimates indicated that MCAR was implausible, we weighted all analyses by the

inverse probabilities from the logistic models of taking part at follow-up, assuming a missing-at-random dropout mechanism [42]. Further, we tested a possible mediating effect of psychotropic medication between lifetime diagnoses of mood disorders and change of pre-existing CVRFs showing no relevant associations. Details can be found in the supplementary material.

A p value of <0.05 was considered statistically significant. Additionally, we applied the Simes–Benjamini–Hochberg procedure [43] to adjust all reported p values for multiple testing [44, 45] and presented q values, which are equivalent to the lowest false discovery rate that could be set to reject the null hypothesis and are also called 'adjusted p values' [44, 45]. Analyses were performed using procedures for complex survey data using Stata 13.1 (Stata Corporation, College Station, TX, USA).

Results

Table 1 displays the baseline characteristics of the study sample. About 15% of participants in the total sample were diagnosed with a history of MDD, with mild MDD being the least prevalent. Participants in the CVRF subsamples were on average older and less educated. Prevalence estimates of CVRF were 29.4% for hypertension, 5.2% for diabetes mellitus, 53.0% for dyslipidemia and 17.4% for obesity. When grouping participants by the diagnosed mood disorder, participants with bipolar disorder showed a high percentage of current smoking (60.8%), prevalent obesity (39.7%) and psychotropic medication use (15.7%) (Supplemental Table 2). The use of psychotropic medication at baseline and follow-up corroborated the assumed gradient of MDD severity, with 2.8% of participants with mild, 4.3% of participants with moderate, and 14.9% of participants with severe MDD using psychotropic medication. Numbers at follow-up followed a similar pattern: 6.1%, 6.6%, and 20.9%.

Table 2 shows coefficients of the linear regression models for the associations between the investigated mood disorders and the examined outcomes of CVRFs at follow-up. In the group of participants with hypertension at baseline, the regression model showed a history of bipolar disorder being associated with a higher systolic blood pressure at follow-up (β: 14.6; 95% CI 4.9–24.4). While a history of any MDD was not associated with blood pressure change at follow-up, we found that a history of moderate MDD was associated with lower systolic (β: − 7.2; 95% CI − 13.3 to − 1.1) and diastolic (β: − 4.4; 95% CI − 7.7 to − 1.1) blood pressure at follow-up when compared to persons without a history of MDD. These coefficients were significantly different from those related to a history of severe MDD ($p<0.01$; adjusted Wald test). In participants with a history of mild or severe MDD and arterial hypertension at baseline, no associations with blood pressure changes at follow-up were found, when compared to participants without a history of MDD.

Whereas, no associations of a lifetime history of MDD or bipolar disorder with follow-up parameters were found in the subsamples with diabetes mellitus or dyslipidemia, a history of severe MDD was weakly associated with a higher BMI at follow-up in the obesity subsample (β: 1.2; CI 0.0–2.4).

Table 3 shows coefficients of regression models investigating outcome changes in the CVRF subsamples considering the use of disease-specific medication. When correcting our models for the use of antihypertensive medication at baseline and follow-up, the observed coefficients changed only slightly and remained statistically significant. Neither a history of MDD nor bipolar disorder was significantly associated with an intensified antihypertensive treatment at follow-up. In the diabetes subsample, a history of moderate MDD was associated with an intensified antidiabetic treatment (RR: 1.77; CI 1.09–2.87). No associations were found in the subsample with dyslipidemia at baseline.

Discussion

Using data from the GHS, this is the first study to examine associations between MDD or bipolar disorder and changes in already clinically manifest CVRFs. Grouping participants by clinically manifest CVRFs at baseline resulted in relatively small sample sizes for prospective analyses. Therefore, the presented results have to be considered exploratory. Summarising our results, we did not find consistent deterioration of CVRFs in persons with compared to persons without MDD or bipolar disorder. Instead, we found heterogenous changes of blood pressure in individuals with arterial hypertension at baseline, while a history of bipolar disorder was associated with a higher systolic blood pressure at follow-up, a history of moderate MDD was associated with a lower blood pressure. These changes were not solely explained by the use of antihypertensive or psychotropic medication. Additionally, we found a weak association of a history of severe MDD with a higher BMI at follow-up. Although we aimed to investigate changes of CVRFs over a long time period by defining lifetime diagnoses of MDD and bipolar disorder as a valid but relatively roughly scaled exposure, we belief that these analyses contribute valuable knowledge for clinical risk assessment (e.g. medical history), treatment planning and further research. Further, our findings regarding the use of psychotropic medication underpin a clinical relevance of lifetime mood disorder diagnoses of different severity even 12 years after the baseline CIDI-interview.

Table 1 Baseline characteristics of the total study sample by cardiovascular risk factors

	Total ($N=1877$)	Subsamples by cardiovascular risk factors			
		Arterial hypertension ($N=541$)	Diabetes mellitus ($N=85$)	Dyslipidemia ($N=929$)	Obesity ($N=326$)
MDD (%)[a]					
Any	15.1	12.6	9.5	14.1	15.0
Mild	3.9	2.7	4.2	3.0	2.0
Moderate	5.7	5.4	2.3	5.0	5.5
Severe	5.5	4.6	3.0	6.0	7.5
Bipolar disorder (%)[b]	1.1	0.6	0.9	1.1	2.5
Women (%)	50.7	52.8	30.1	47.0	53.6
Age (years)	45.6 (13.4)	52.5 (10.4)	54.8 (8.5)	48.4 (12.2)	49.4 (11.5)
School (%)					
< 10 years	43.1	51.2	63.8	47.2	59.3
= 10 years	33.4	30.8	22.3	31.9	25.4
> 10 years	23.5	17.9	14.0	20.9	15.3
Smoking status (%)					
Never-smoker	49.6	55.9	47.3	49.3	49.3
Ex-smoker	23.0	26.6	27.2	23.5	26.9
Current smoker	27.4	17.6	25.4	27.3	23.8
Alcohol consumption (g/day)	10.0 (17.5)	10.8 (16.8)	7.8 (12.5)	9.4 (16.4)	8.6 (15.9)
Art. hypertension (%)	29.4	–	62.7	36.0	52.2
Systolic blood pressure (mmHg)	127.6 (16.8)	142.4 (16.9)	139.3 (18.8)	130.1 (16.1)	134.1 (16.1)
Diastolic blood pressure (mmHg)	78.3 (9.8)	86.4 (9.5)	82.6 (9.7)	79.9 (9.2)	82.5 (8.8)
Use of antihypertensive medication (%)	11.8	40.4	30.3	16.5	22.6
Diabetes (%)	5.2	11.0	–	6.3	10.1
HbA1c (%)	5.4 (1.3)	5.7 (1.4)	7.7 (1.8)	5.5 (1.2)	5.7 (1.3)
Use of antidiabetics (%)	2.6	5.7	49.9	2.4	3.7
Dyslipidemia (%)	53.0	64.5	64.3	–	66.7
LDL-C (mmol/l)	3.8 (1.2)	4.1 (1.1)	3.9 (1.0)	4.4 (1.2)	4.0 (1.1)
HDL-C (mmol/l)	1.5 (0.5)	1.5 (0.5)	1.4 (0.4)	1.4 (0.5)	1.3 (0.4)
TG (mmol/l)	1.5 (0.9)	1.7 (1.0)	1.9 (1.1)	1.8 (0.9)	2.0 (1.0)
Use of statins/fibrates (%)	3.6	6.0	17.0	6.8	3.9
Obesity (%)	17.4	30.6	32.2	22.0	–
BMI (kg/m^2)	26.5 (5.0)	28.6 (5.3)	29.8 (6.3)	27.4 (4.6)	33.6 (4.9)
Use of psychotropic medication (%)	4.6	5.5	3.8	5.2	6.4

HbA1c, haemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; TG, triglycerides; BMI, body mass index

Values are weighted means (standard deviation) for continuous variables and weighted percentages for categorical variables

[a]Lifetime CIDI-diagnosed major depressive disorder

[b]Lifetime CIDI-diagnosed bipolar I disorder or Bipolar II Disorder

Previous studies

On one hand, mood disorders are associated with the development of cardiovascular disease [5–7, 18, 46] and an increased cardiac mortality [47, 48]. On the other hand, meta-analyses of the data on CVRFs in people with MDD showed inconsistent results: a study investigating late life depression (> 50 years) reported no higher risks for arterial hypertension (odds ratio, OR 1.14; 95% CI 0.94–1.40) or dyslipidemia (OR 1.08; 95% CI 0.91–1.28), but for diabetes (OR 1.51; 95% CI 1.30–1.76) [18]. Other meta-analyses investigating relations with MDD reported similar findings with higher risks for diabetes (RR 1.49; 95% CI 1.29–1.72) [13] and hypertriglyceridemia (OR 1.17; 95% CI 1.04–1.30) [12] but not for hypertension (OR 0.89; 95% CI 0.62–1.28) [12] and lowered HDL-C (OR 1.41; 95% CI 0.94–2.12) [12].

However, these results are based on data comparing incidence rates of CVRFs. Interpreting our results in the context

Table 2 Associations between lifetime prevalence of different mood disorders and hypertension, diabetes, dyslipidemia or obesity at baseline with corresponding parameters at follow-up

	Arterial hypertension ($N=541$)		Diabetes mellitus ($N=85$)	Dyslipidemia ($N=929$)			Obesity ($N=326$)
	Sys. RR	Dia. RR	HbA1c	LDL-C	HDL-C	TG	BMI
	β (95% CI) *p* value *q* value[a]	β (95% CI) *p* value *q* value[a]	β (95% CI) *p* value *q* value[a]	β (95% CI) *p* value *q* value[a]	β (95% CI) *p* value *q* value[a]	β (95% CI) *p* value *q* value[a]	β (95% CI) *p* value *q* value[a]
No MDD	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Any	− 1.3 (− 5.3–2.7) *p* = 0.52 *q* = 0.82	− 1.4 (− 3.9–1.0) *p* = 0.25 *q* = 0.65	0.3 (− 0.1–0.8) *p* = 0.14 *q* = 0.65	− 0.0 (− 0.2–0.2) *p* = 0.89 *q* = 0.95	0.0 (− 0.0–0.1) *p* = 0.87 *q* = 0.95	− 0.0 (− 0.2–0.2) *p* = 0.97 *q* = 0.98	0.5 (− 0.4–1.5) *p* = 0.28 *q* = 0.65
Mild	1.8 (− 8.9–12.5) *p* = 0.74 *q* = 0.95	− 1.3 (− 6.5–3.9) *p* = 0.62 *q* = 0.86	0.6 (− 0.3–1.6) *p* = 0.21 *q* = 0.65	0.2 (− 0.2–0.7) *p* = 0.25 *q* = 0.65	− 0.0 (− 0.1–0.0) *p* = 0.47 *q* = 0.82	0.0 (− 0.3–0.3) *p* = 0.98 *q* = 0.98	0.1 (− 1.4–1.6) *p* = 0.88 *q* = 0.95
Moderate	**− 7.5** (− 13.2 – − 1.9) ***p* = 0.009** *q* = 0.14	**− 4.5** (− 7.8 – − 1.3) ***p* = 0.007** *q* = 0.14	0.5 (− 0.2–1.2) *p* = 0.17 *q* = 0.65	− 0.1 (− 0.4–0.2) *p* = 0.55 *q* = 0.82	0.0 (− 0.0–0.1) *p* = 0.33 *q* = 0.66	− 0.2 (− 0.6–0.2) *p* = 0.39 *q* = 0.71	− 0.4 (− 2.2–1.4) *p* = 0.68 *q* = 0.90
Severe	4.2 (− 0.7–9.2) *p* = 0.09 *q* = 0.56	2.3 (− 1.4–6.0) *p* = 0.22 *q* = 0.65	− 0.1 (− 0.7–0.5) *p* = 0.77 *q* = 0.95	− 0.1 (− 0.3–0.2) *p* = 0.50 *q* = 0.82	− 0.0 (− 0.1–0.1) *p* = 0.82 *q* = 0.95	0.2 (− 0.1–0.4) *p* = 0.31 *q* = 0.66	**1.2** (0.0–2.4) ***p* = 0.047** *q* = 0.39
Bipolar disorder	**14.6** (4.9–24.4) ***p* = 0.004** *q* = 0.14	5.6 (− 2.9–14.2) *p* = 0.19 *q* = 0.65	0.8 (− 0.1–1.7) *p* = 0.07 *q* = 0.48	0.2 (− 0.5–0.9) *p* = 0.57 *q* = 0.82	− 0.1 (− 0.2–0.0) *p* = 0.27 *q* = 0.65	− 0.2 (− 0.7–0.3) *p* = 0.50 *q* = 0.82	− 1.4 (− 3.9–1.2) *p* = 0.29 *q* = 0.65

Full adjustment included respective baseline measurement, age, sex, years of schooling, alcohol consumption and smoking. One regression model was run for each outcome

Sys. RR, systolic blood pressure; Dia. RR, diastolic blood pressure; HbA1c, haemoglobin A1c; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; TG, triglycerides; BMI, body mass index, *β*, coefficient from IPW weighted regression; CI, confidence interval

[a]*q* values are equivalent to the lowest false discovery rate that could be set to reject the null hypothesis and are also called 'adjusted *p* values'

of the published literature, it is important to stress that we aimed to investigate changes of already prevalent CVRFs at baseline to identify specific sub-populations at risk for cardiovascular disease. The standardised prevalence rates of CVRFs in our study sample were consistent with epidemiological data [49–52].

The finding that participants with mild or moderate MDD did not show worsened CVRFs over time is particularly interesting. On the contrary, participants with a history of a moderate MDD presented with associations with lower blood pressure at follow-up compared to participants without a history of MDD. Although these findings should not be overstated, these observations partly concur with existing evidence from research investigating relationships between blood pressure and MDD: besides prospective studies reporting no associations with blood pressure [53, 54], reports from cross-sectional [55–57] and prospective analyses [58, 59] observed lower blood pressure in depressed patients.

Besides numerous hypothesised explanatory neurobiological mechanisms (e.g. neuropeptide Y [58]), the associations with lower blood pressure at follow-up might partly be explained by higher levels of a perceived need for help [60] and probably also increase medical help-seeking due to the symptoms of a moderate MDD. An increased use of health care services, especially of general practitioners, could potentially outweigh any negative interrelations of lifetime diagnosed moderate MDDs with the progression of hypertension. Although a history of moderate MDD was not significantly associated with an intensified antihypertensive treatment at follow-up, the association with an intensified antidiabetic treatment might point to an increased use of health care services like general practitioners.

Table 3 Associations adjusted for disease-specific medication between lifetime prevalence of MDD or bipolar disorder and CVRFs at baseline with corresponding parameters at follow-up and associations with an intensified treatment at follow-up

	Arterial hypertension ($N=541$)			Diabetes mellitus ($N=85$)	Dyslipidemia ($N=929$)			
	Systolic BP	Diastolic BP	Intensified treatment	Intensified treatment	LDL-C	HDL-C	TG	Intensified treatment
	β (95% CI) p value q value[a]	β (95% CI) p value q value[a]	RR (95% CI) p value q value[a]	RR (95% CI) p value q value[a]	β (95% CI) p value q value[a]	β (95% CI) p value q value[a]	β (95% CI) p value q value[a]	RR (95% CI) p value q value[a]
No MDD	Ref	Ref	Ref					
Any	− 1.3 (− 5.3 to 2.6) $p=0.50$ $q=0.82$	− 1.4 (− 3.7 to 0.9) $p=0.22$ $q=0.65$	1.01 (0.79–1.31) $p=0.90$ $q=0.95$	1.15 (0.64–2.08) $p=0.63$ $q=0.86$	− 0.0 (− 0.2 to 0.1) $p=0.71$ $q=0.93$	0.0 (− 0.0 to 0.1) $p=0.82$ $q=0.95$	− 0.0 (− 0.3 to 0.2) $p=0.92$ $q=0.95$	0.98 (0.63–1.52) $p=0.92$ $q=0.95$
Mild	1.2 (− 9.7 to 12.1) $p=0.82$ $q=0.95$	− 1.5 (− 6.5 to 3.4) $p=0.53$ $q=0.82$	1.22 (0.81–1.82) $p=0.33$ $q=0.66$	1.05 (0.52–2.11) $p=0.89$ $q=0.95$	0.2 (− 0.1 to 0.5) $p=0.26$ $q=0.65$	− 0.0 (− 0.1 to 0.1) $p=0.57$ $q=0.82$	− 0.0 (− 0.3 to 0.2) $p=0.86$ $q=0.95$	0.47 (0.16–1.40) $p=0.17$ $q=0.65$
Moderate	**−6.7** (− 12.2 to − 1.2) **$p=0.017$** $q=0.22$	**−4.1** (− 7.2 to − 1.1) **$p=0.008$** $q=0.14$	1.19 (0.87–1.62) $p=0.28$ $q=0.65$	**1.77** (1.09–2.87) **$p=0.022$** $q=0.22$	− 0.1 (− 0.3 to 0.2) $p=0.48$ $q=0.82$	0.0 (− 0.0 to 0.1) $p=0.32$ $q=0.66$	− 0.2 (− 0.6 to 0.2) $p=0.38$ $q=0.71$	1.08 (0.52–2.21) $p=0.84$ $q=0.95$
Severe	3.5 (− 0.8 to 7.9) $p=0.11$ $q=0.63$	2.0 (− 1.3 to 5.3) $p=0.24$ $q=0.65$	0.68 (0.41–1.14) $p=0.14$ $q=0.65$	0.38 (0.07–2.19) $p=0.28$ $q=0.65$	− 0.1 (− 0.3 to 0.1) $p=0.36$ $q=0.70$	− 0.0 (− 0.1 to 0.1) $p=0.83$ $q=0.95$	0.2 (− 0.2 to 0.5) $p=0.32$ $q=0.66$	1.17 (0.64–2.15) $p=0.61$ $q=0.86$
Bipolar disorder	**16.2** (2.2 to 30.1) **$p=0.024$** $q=0.22$	6.5 (− 4.7 to 17.6) $p=0.25$ $q=0.65$	0.92 (0.22–3.87) $p=0.90$ $q=0.95$	–[b]	0.4 (− 0.0 to 0.8) $p=0.07$ $q=0.48$	− 0.1 (− 0.2 to 0.0) $p=0.16$ $q=0.65$	− 0.1 (− 0.6 to 0.4) $p=0.57$ $q=0.82$	2.13 (0.73–6.20) $p=0.16$ $q=0.65$

Adjustment included respective baseline measurement (linear regressions), age, sex, years of schooling, alcohol consumption and smoking. One regression model was run for each outcome

Systolic bp, systolic blood pressure; Diastolic bp, diastolic blood pressure; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; TG, triglycerides; β, coefficient from IPW weighted regression analysis adjusted for the use of disease-specific medication at baseline and follow-up; RR, relative risks from weighted Poisson regression investigating associations with an intensified CVRF treatment at follow-up; CI, confidence interval

[a]q values are equivalent to the lowest false discovery rate that could be set to reject the null hypothesis and are also called 'adjusted p values'

[b]Due to zero variance of the outcome a statistical analysis in our model was not possible

Nabi et al. reported findings from the Whitehall II prospective cohort study with five consecutive medical examinations of blood pressure and depressive symptoms, considering the fluctuation of depressive symptoms over time; while participants with "increasing depression" had a 24% lower risk of hypertension at ages 35–39 years, they showed a faster age-related increase in hypertension (7% greater odds for each 5-year increase in age) [61]. Explaining these findings, Nabi et al. hypothesised that the faster age-related increase in hypertension "could be seen as a consequence of depressive symptoms that are likely to be persistent, severe, or less responsive to treatment" [61]. This hypothesis converges with evidence from longitudinal studies reporting greater risk for hypertension in people with depressive symptoms [62–65]. Although we did not find a statistically significant association of a history of severe MDD with a higher systolic blood pressure at follow-up (CI − 0.7 to 9.2), coefficients differed considerably from those with a history of moderate MDD, pointing to severity of MDD as a potential correlate of long-term changes of arterial hypertension. In line with these findings, Lamers et al. found the baseline severity of the MDD being the most important differentiator in course between groups of melancholic and atypical subtypes of MDD when investigating a 6-year longitudinal psychiatric and somatic course [66]. In addition, our analyses match reports from cross-sectional analyses that showed an even higher risk for hypertension in people diagnosed with bipolar I disorder compared to people with MDD [6]. Accordingly, a history of bipolar disorder and comorbid hypertension might be particularly harmful.

Further research is needed to clarify the impact of a history of severe MDD on blood pressure changes in people with arterial hypertension.

Regarding obesity, a large systematic review and meta-analysis on the longitudinal relationship between depression and obesity confirmed a reciprocal link between incidence rates of both conditions [67]. In our sample, obesity at baseline emerged as a CVRF clearly related to the severity of the mood disorder: 39.7% of participants in the bipolar disorder subsample, 23.6% in the severe MDD subsample, 16.9% in the moderate and 8.9% in the mild MDD subsample were obese. Although only a weak association with BMI at follow-up was found, our analyses point towards a deterioration of obesity especially in participants with a history of severe MDD. While data on the progression of pre-existing dyslipidemia in people with MDD are scarce and the interpretation of triglyceride serum levels in our study is limited since we used a non-fasting population sample, our results fit reports from cross-sectional [68, 69] and prospective [69, 70] clinical studies that found no association between depressive symptom severity and HbA1c levels in people with comorbid MDD and diabetes mellitus.

There is evidence that presence of CVRFs in persons with depression is mediated by use of antidepressants [71]. When analysing this population-based cohort data, we found no distinctive mediation effects of antidepressants on changes of pre-existent CVRFs. However, since we have no data on the continuous use of any medication over the 12-year study period, these results should be interpreted cautiously.

Strengths and limitations

Among the strengths of our study is a large and representative baseline population sample with a comprehensive and quality-assured assessment with respect to continuous parameters of CVRFs, psychiatric symptoms of mood disorders and the availability of follow-up measurements. Although the sample for prospective analyses was smaller ($n = 1887$), the sample size was still considerable. However, several important methodological limitations need to be considered. First, only participants aged 65 years or less at baseline have been included in our study due to lack of validity of the CIDI-interview for this age group. Second, for our analysis we used a lifetime CIDI-diagnosis of mood disorders to baseline, therefore, not allowing conclusions concerning prevalent symptoms of mood disorder at baseline or within the follow-up period. Third, since there is a growing body of cross-sectional ([72–75]) and longitudinal ([66, 76]) evidence that a subtyping of MDD into atypical and melancholic can be important when investigating differential associations between these two depression subtypes and CVRFs, it is important to note that the available data for this study did not allow a comparable subtyping of MDD. Fourth, since we used a non-fasting population sample the interpretation of triglyceride serum levels is limited and should not be overstated. Fifth, it is important to stress that gender differences in the prevalence of mood disorders as well as in health care service use are important and are also present in the current paper (women in the subsample reporting any history of MDD: 70.9%). Relations of these differences with mood disorders and changes of CVRFs warrant further investigation. Sixth, when designing our study, we had to balance the risk of multiple testing with a broad approach on investigating more than one CVRF. Since this is the first study investigating associations between MDD or bipolar disorder and changes in already clinically manifest CVRFs, we decided to perform an exploratory study reporting data on four CVRFs. However, the exploratory nature of our findings is also underlined by generally high q values pointing to a considerable risk for incorrectly rejecting the null hypothesis due to multiple testing. Seventh, when adjusting for CVRF-specific medication and evaluating changes of CVRF-specific medication at follow-up, we did not adjust HbA1c levels and no data on doses were used. An intensified treatment at follow-up was defined by new or additional CVRF-specific agents at follow-up. Finally, although we addressed drop-out that can be explained by measured baseline covariates (i.e., assuming MAR using a weighting scheme), participants who did not take part at the follow-up might have experienced change of their health status since baseline, which could be related to mood disorder or CVRFs and lead to non-negligible dropout introducing selection bias towards more favourable outcomes.

Conclusion

Participants with a lifetime history of MDD in this cohort did not carry a specific risk for a worsening of pre-existing clinically manifest CVRFs. Our explorative findings point to bipolar disorder and the severity of MDD as important correlates of long-term changes of arterial hypertension and obesity. We speculate that differences in nature of diseases [77], episode duration and medical help-seeking are the most likely causes for these findings. As most investigated follow-up parameters were not associated with a lifetime history of the investigated mood disorders, clinical surveillance of arterial hypertension and obesity could be particularly beneficial for people with a history of severe mood disorders. Thus, for a deeper understanding of implications of mood disorders on the long-term changes of CVRFs, the consideration of affective symptom severity and nature of diseases seems important and might help to disentangle the mixed findings of research linking CVRFs to mood disorders. Since the longitudinal investigation of changes of already clinically manifest CVRFs in people with mood disorders requires large

epidemiological samples with combined thorough physical and psychiatric measures, the current underlying evidence is scarce. Thus, further prospective and experimental studies are warranted to confirm these observations and to identify causal relationships.

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Compliance with ethical standards

Conflict of interest All authors report no conflict of interest.

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