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Association between major depression and type 2 diabetes in mid-life: Findings from the Screening Across the Lifespan Twin Study

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Abstract

Objective—Cohort studies suggest that the relationship between major depression (MD) and type 2 diabetes (T2DM) is bi-directional. However, this association may be confounded by shared genetic or environmental factors. The objective of this study was to use a twin design to investigate the association between MD and T2DM.

Methods—Data come from the Screening Across the Lifespan Twin Study, a sample of monozygotic and dizygotic twins aged 40 sampled from the Swedish Twin Registry (N=37,043). MD was assessed using the Composite International Diagnostic Inventory. Structural equation twin modeling and Cox proportional hazards modeling were used to assess the relationship between MD and T2DM.

Results—Approximately 19% of respondents had a history of MD and 5% had a history of T2DM. MD was associated with 32% increased likelihood of T2DM (95% Confidence Interval: 1.00 – 1.80) among twins aged 40 – 55 even after accounting for genetic risk, but was not associated with T2DM among twins >55 years. T2DM was associated with 33% increased likelihood of MD (95% CI: 1.02 – 1.72) among younger, but not older twins. Cholesky decomposition twin modeling indicated that common unique environmental factors contribute to the association between MD and T2DM.

Conclusions—Environmental factors that are unique to individuals (e.g., not shared within families), but common to both MD and T2DM contribute to their co-occurrence in mid-life. However, we cannot exclude the possibility of bi-directional causation as an alternate explanation.

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It is likely that multiple processes are operating to affect the relation between psychological and medical conditions in mid-life.

Keywords

depression; type 2 diabetes; aging; comorbidity; epidemiology

INTRODUCTION

One of the hallmarks of major depression (MD) in mid- and late-life is the co-occurrence of medical conditions, particularly chronic diseases such as type 2 diabetes (T2DM) and cardiovascular disease (1,2). MD is associated with both incidence of and mortality from T2DM (3–5), and clinically-identified T2DM is associated with risk of MD (3,6).

Antidepressant medications have also been associated with development of T2DM (7–9), although confounding by indication remains a critical limitation of these studies (10).

There are three broad conceptual models that could explain the association between MD and T2DM (11): [1] (bi-)directional phenotypic causation, whereby MD increases risk of T2DM (and vice versa) through biological or behavioral pathways, [2] shared genetic liability, whereby the co-occurrence of MD and T2DM is due to common genetic factors, and [3] shared environmental liability, whereby the co-occurrence of MD and T2DM is due to environmental exposures that increase risk for both conditions. Shared environmental liability may occur either because of environmental factors that are nested within families (so called “common” environmental factors), or because of environmental factors that are unique to individuals (e.g., occur to one twin but not the other) but predict both MD and T2DM (e.g., are not shared within families, but are factors that themselves act a common cause of both conditions). In the latter two scenarios, there is no causal relationship between MD and T2DM; instead shared risk factors explain why these two conditions co-occur. Both MD and T2DM have substantial genetic components, with heritability estimates on the order of 30% to 40% for MD (12) and range from 26% to 69% for T2DM, with earlier onset associated with greater genetic risk for both conditions (13–15).

Therefore, while population-based cohort studies have suggested that the relationship between MD and T2DM is bi-directional, this association may be confounded by unmeasured genetic or environmental factors common to both conditions. For example, recent evidence indicates that while there is a bi-directional relationship between MD and coronary artery disease, shared environmental factors are also relevant for this comorbidity among men, and shared genetic factors are relevant among women (16). Similarly, Xian and colleagues (2010) reported that genetic vulnerability to MD, in addition to the actual experience of MD, is an important risk factor for ischemic heart disease (17). Finally, McCaffery and colleagues (2003) found that shared environmental factors explain the covariance between depressive symptoms and markers of metabolic risk (e.g., plasma glucose, triglycerides, waist-hip ratio) (18).

Twin studies, which model sources of resemblance between individuals matched on both genetic liability and family environment, offer a means to resolve these competing explanations of the co-occurrence of psychiatric and medical conditions. In the only prior

study to examine the association between MD and T2DM using a twin design, Sherrer and colleagues (2011) found no evidence that the co-occurrence of elevated depressive symptoms, as measured by the Short Form-36, and T2DM was due to either shared genetic or environmental factors, consistent with the bi-directional phenotypic causation model outlined above (19). However, this study had a relatively small sample and used a non-diagnostic measure of depressive symptoms. Thus, it remains unresolved whether shared genetic or environmental risk factors explain the co-occurrence of MD and T2DM in mid- and late-life.

The goal of this study was to investigate whether common genetic and environmental factors contribute to the association between MD and T2DM using a large population-based twin sample. A better understanding the processes that link MD to T2DM may inform prevention and treatment efforts for both these conditions.

METHODS

Sample

The Screening Across the Lifespan Twin (SALT) Study is a cross-sectional population-based sample drawn from the Swedish Twin Registry. The SALT cohort consists of monozygotic (MZ) and same and opposite-sex dizygotic (DZ) twin pairs age 40 and over in 1998 (born in 1958 or earlier) drawn from general population birth records. Details of SALT and additional characteristics of the sample have been described elsewhere (20,21). Briefly, interviews were conducted between 1998 and 2002 by telephone and the overall participation rate was 73.6%. Zygosity was confirmed using validated twin physical resemblance questionnaires. The total SALT sample consists of 44,919 individuals. This analysis is restricted to 37,043 individuals with known zygosity and complete data on MD and T2DM status, representing 13,744 complete twin pairs (3,342 MZ pairs and 10,402 same and opposite-sex DZ pairs). The average age of the analytic sample was 59.0 years (SD: 10.9).

The SALT study is approved by Ethics Committee at the Karolinska Institutet and all participants provided informed consent. This secondary data analysis received exempt status from the VCU Institutional Review Board.

Measures

Lifetime history of major depression (MD) was assessed using the Short-form Composite International Diagnostic Inventory (CIDI), a fully-structured diagnostic instrument administered by lay interviewers that operationalizes the Diagnostic and Statistical Manual of Mental Disorders –IV criteria for MD (22). The CIDI has moderate concordance (sensitivity ranging from 50–100% and specificity ranging from 46–89%) with clinical psychiatric interviews (23). Diabetes status was assessed by self-report of physician diagnosis, diabetes type (1 or 2), and age of onset; type 1 diabetes cases were excluded from analysis (N=207). In instances where MD or T2DM status was known (i.e., present or absent) but age of onset was not (2,455 cases of MD and 39 cases of T2DM), multiple imputation was used to estimate an age of onset for these cases (Table S1, Supplemental

Digital Content 1). Analyses restricting the sample to those with complete data on age of MD and T2DM onset were comparable to the results reported here (data not shown). Birth weight (available on 16,975 individuals) was assessed by self-report and categorized as very low (<1500g), low (1500 to <2500g) and normal (≥2500g), reflecting the fact that twins tend to have lower birth weight than singletons. All covariates were assessed by self-report.

Analysis

First, Cox proportional hazards models were used to assess the bi-directional relationship between MD and T2DM, consistent with prior epidemiologic work on this comorbidity (3). Initial analyses indicated that correlation between MD and T2DM declined with age (Figure S1, Supplemental Digital Content 1), and thus age was categorized into middle-aged (41 – 55 years, 45% of the sample) and older adults (>55 years). Results for the older adult group with further restriction to adults aged 65 and older were consistent with the >55 year models (data not shown). Models were adjusted for age, sex, and genetic risk for the outcome. In these regression analyses, genetic risk for the outcome (MD or T2DM) was indexed by a 4-level variable that reflected the genetic similarity (e.g., MZ twins share 100% of their genes identical by descent, and DZ twins share 50%) and health status of each individual's co-twin; this implies that the genetic component is genetic in nature if the correlation for MZ twins is approximately twice the correlation of DZ twins. –1 for MZ twins whose co-twin did not have MD (or T2DM, depending on the analysis), –0.5 for DZ twins whose co-twin did not have MD (or T2DM), +0.5 for DZ twins whose co-twin had a positive history of MD (or T2DM), and +1 for MZ twins whose co-twin had a positive history of MD (or T2DM). Appropriateness of the proportional hazards assumption was assessed by visual inspection of the hazard plots. Finally, risk of MD and T2DM varies by both gender and birth weight (3, 24, 25), and thus as an exploratory aim we investigated whether the MD-T2DM relationship varied by sex or birth weight using stratified analyses.

Next, structural equation twin modeling was used to estimate the contributions of additive genetic (A), shared environmental (C) and unique (E) environmental influences to the liability of MD and T2DM (26). The twin study design is based on the comparison of similarities between MZ and DZ twin pairs. MZ twins share 100% of their genes while DZ twins share on average 50% of their genes. A greater difference in measures of similarity between MZ and DZ pairs suggests the presence of additive genetic influences on a trait. Shared (C) environmental effects make members of the twin pair relatively more similar, whereas unique (E) environmental factors contribute to differences between members of the twin pairs.

We first estimated the additive genetic, shared environment, and unique environment contributions to MD and T2DM using bivariate structural equation twin models. Next, we extended this bivariate modeling approach to evaluate the magnitude of the relationship between MD and T2DM, as well as the degree to which shared genetic and environmental factors contributed to their co-occurrence (26). In this approach, a bivariate Cholesky model was used to decompose the genetic and environmental contributions to MD and T2DM into [1] elements that uniquely contribute to the variance of MD, [2] elements that uniquely contribute to the variance of T2DM, and [3] elements that contribute to the covariance of

MD and T2DM (Figure S2, Panel A, Supplemental Digital Content 1). Standardized covariances were estimated to indicate the degree to which genetic, shared environmental, and unique environmental factors explain the correlation between MD and T2DM. The sum of these standardized genetic and environmental covariances is equal to the phenotypic correlation between MD and T2DM (26).

Finally, we compared the Cholesky decomposition model to the bi-directional phenotypic causation model within the twin structural equation modeling framework (11). Based on methods described elsewhere (27), we fit a set of three of unidirectional and reciprocal causation models ($MD \leftrightarrow T2DM$, $MD \rightarrow T2DM$ and $T2DM \rightarrow MD$) (Figure S2, Panel B, Supplemental Digital Content 1). These models were not nested within the Cholesky decomposition model (i.e., a model with both direction of causation and the decomposition of variance was not identified), but instead were used to estimate the confidence with which we could reject or support the direct phenotypic causation hypothesis. All twin models were adjusted for the mean effects of age and sex. Goodness-of-fit statistics (i.e., $-2\log$ -likelihood and Akaike's information criterion) were used to identify the best fitting model.

Analyses were conducted using SPSS (v21) and R (v2.15.2). Twin structural equation modeling was implemented using the OpenMx package in R (v1.3) (28,29).

RESULTS

Overall, 19.4% of respondents had a lifetime history of MD, with an average age of onset of 40.6 years (SD: 12.2); 4.7% had a history of T2DM, with an average age of onset of 57.3 years (SD: 12.6) (Table 1). In the entire sample, there was no association between MD and T2DM after adjusting for age (Odds Ratio (OR): 1.07, 95% CI: 0.95 – 1.22 and Table S3, Supplemental Digital Content 1), and the cross-twin, cross-trait correlations ($r_{MZ_{men}}: -0.13$, $r_{DZ_{men}}: 0.06$, $r_{MZ_{women}}: -0.04$, $r_{DZ_{women}}: -0.06$) were near-zero, indicating that MD status of a twin was essentially uncorrelated with the T2DM status of their co-twin. However, in age-stratified analyses MD was positively associated with T2DM among middle-aged (aged 40 – 55) but not older twins (Table 2).

We first examined the relationship between MD and T2DM using Cox proportional hazards models to leverage age of onset data as an indicator of temporal ordering (Figure 1; plots for the older twins are shown in Figure S3, Supplemental Digital Content 1). As shown by Table 3, MD was associated with 49% increased risk of T2DM among middle-aged twins, but this association was substantially attenuated after accounting for genetic risk of T2DM, and the confidence interval in the fully-adjusted model included one. As shown by the lower panel of Table 3, in the middle-aged twins T2DM was associated with 1.33 times increased likelihood of MD (95% Confidence Interval: 1.02 – 1.72) after accounting for genetic liability for MD. There was no evidence that the relationship between either MD and onset of T2DM, or T2DM and onset of MD, varied by birth weight (Table S2, Supplemental Digital Content 1). In gender-stratified analyses, MD was significantly associated with onset of T2DM among women (Hazard Ratio (HR): 1.74, 95% CI: 1.09 – 2.79) but not men (HR: 1.08, 95% CI: 0.70 – 1.67) in the middle-aged twins, even after accounting for genetic risk for T2DM. Similarly, T2DM was associated with risk of MD among women (HR: 1.49,

95% CI: 1.04 – 2.12) but not men (HR: 1.21, 95% CI: 0.83 – 1.78) among the middle-aged twins. Among the older twins, there was no gender difference in the relationship between MD and risk of T2DM (HR_{women}: 0.92, 95% CI: 0.72 – 1.18 and HR_{men}: 1.17, 95% CI: 0.87 – 1.57), or T2DM and risk of MD (HR_{women}: 0.94, 95% CI: 0.75 – 1.19 and HR_{men}: 1.18, 95% CI: 0.88 – 1.57).

We then employed twin structural equation models to examine the genetic and environmental contributions to the association between MD-T2DM. First, we fit bivariate structural equation twin models to estimate the A, C, and E components to MD and T2DM among the middle-aged subsample of twins. The most parsimonious bivariate model for both MD and T2DM was one that included the effects of both additive genetic and unique environmental factors (AE) (Table S4, Supplemental Digital Content 1), consistent with previous research (19). The estimates of the heritability for MD (44%) and T2DM (82%) were also consistent with prior reports (12,14). The amount of the total variance due to A for MD was 0.42 (95% Confidence Interval (CI): 0.32 – 0.51), and unique environmental factors accounted for 0.58 (95% CI: 0.47 – 0.68) of the total variance. For T2DM, the amount of the total variance due to A was 0.87 (95% CI: 0.68 – 0.88), and unique environmental factors accounted for 0.13 (95% CI: 0.05 – 0.32) of the total variance.

We then assessed the Cholesky decomposition model. There was a significant phenotypic correlation between MD and T2DM (r : 0.20; 95% CI: 0.09 – 0.33), as expected from the Cox regression analyses. The genetic contribution to this association was non-significant (covA: 0.05; 95% CI: –0.12 – 0.21), indicating that the genetic factors that influence MD are not the same as those that influence T2DM. The final Cholesky bivariate genetic model (Figure 2) indicated that this association was due to significant covariance in unique environmental factors between MD and T2DM (covE: 0.15; 95% CI: 0.01 – 0.30). The environmental covariance reflected moderate overlap between unique environmental influences shared between MD and T2DM (r_E : 0.54; 95% CI: 0.02 – 0.88), suggesting that environmental exposures that increase risk of MD also increase the likelihood of T2DM.

Finally, we compared the Cholesky twin model from Figure 2 to the direction of causation models (bi-directional, MD→T2DM and T2DM→MD). The fit statistics from these models are shown in Table 3. There was no significant difference between the bidirectional model or either of the unidirectional models when compared to the Cholesky model. That is, there was no evidence that a phenotypic causation model fit the data better (or worse) than the correlated environmental (E) risk factors model from the Cholesky decomposition.

DISCUSSION

The results of this study suggest that environmental risk factors shared by both MD and T2DM contribute to the observed association between MD and T2DM in mid-life. Our results are consistent with those reported by Sherrer and colleagues (19) which indicated that there is no significant genetic correlation between MD and T2DM. These relationships appear to be stronger in mid-life (40–55 years old) than in later life (>55 years). This is the largest study to date to investigate the co-occurrence of MD and T2DM using a genetically-

informative design, and our findings add to growing body of evidence of the nature of the epidemiologic associations between MD and cardiometabolic conditions.

The finding that environmental factors contribute to the co-occurrence of both MD and T2DM has not been reported previously. This is consistent with an interpretation that the reason MD and T2DM co-occur is because they are both caused by a similar set of unique (e.g., E paths in the twin models) environmental risk factors, but that these environmental factors do not reflect characteristics of the family environment shared by twins (e.g., C paths). One of the most well-established unique environmental risk factors for MD from twin studies is exposure to stress (15), and there is a growing body of evidence suggesting that stress exposure has pluripotent implications for health in later life (30). For example, chronic social stress is an established risk factor for MD (31), and numerous studies indicate that social stress is also associated with alterations in physiologic systems (e.g., inflammation, glucose metabolism) (32,33) that increase risk of T2DM (34,35). Allostatic load has been suggested as one mechanism by which chronic stress exposure may increase risk of cardiometabolic conditions in mid-life (36), but it may also be that stress exposure prompts the use of unhealthy behaviors (e.g., cigarette smoking, diets high in fats and sugar, alcohol use) that in turn increase risk of T2DM (and also potentially MD) (37,38). Longitudinal studies are needed to further understand the shared behavioral and biological processes that increase risk of both MD and T2DM.

Although our findings support the hypothesis that unique environmental risk factors common to both conditions contribute to the association between MD and T2DM, we had limited ability to differentiate this model from one of bi-directional causation, and our regression analyses indicate that there is some residual direct phenotypic relationship after accounting for genetic risk. Thus, we cannot exclude the possibility that part of the association between MD and T2DM results from bi-directional phenotypic causal processes. However, the mechanisms linking MD to subsequent T2DM are likely different than those linking T2DM to subsequent MD. MD has been associated with abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, particularly regulation of cortisol (39,40). Hypercortisolism is an established risk factor for insulin resistance (41). MD is also associated with abdominal as opposed to visceral deposition of fat, which is also correlated with diabetes risk (42). Finally, MD is associated with engagement in poor health behaviors, including smoking, alcohol misuse, and physical inactivity, all established risk factors for T2DM (43). For MD subsequent to T2DM, however, it is likely that factors related to behavioral and psychological coping are more relevant. Numerous studies have now shown that only clinically-identified T2DM is associated with higher likelihood of MD, whereas undiagnosed T2DM is largely unrelated to MD (44). This indicates that there is not a biological link between clinical features of T2DM (e.g., obesity, hyperglycemia, hyperinsulinemia) but rather that MD develops as a result of diabetes distress and or stress surrounding self-management behaviors (45). Indeed, a recent international study indicated that approximately 40% of individuals with T2DM report significant diabetes-related distress (45).

These findings should be interpreted in light of study limitations. Although we leveraged data on age of onset for MD and T2DM to investigate the bi-directionality of this

relationship, because of the cross-sectional nature of the study we had to reply on retrospective recall of age of onset. Cross-sectional recall of MD tends to underestimate lifetime prevalence (46), although the lifetime prevalence of MD in our sample (19%) was consistent with cumulative incidence estimates from US samples of similar age (46). Second, there was no association between MD and T2DM among the older twins; this was unexpected, although it is consistent with a recent report on MD and T2DM (47); this null relationship may in part reflect survival bias (e.g., MD is associated with higher risk of diabetes-related mortality (48,49)). Despite our large sample size, we had limited statistical power to differentiate the full bivariate model from the direct phenotypic causation models. As a result, we cannot definitively reject the hypothesis that the relationship between MD and T2DM is due to direct causal effects of MD on T2DM, and T2DM on MD. T2DM was assessed by self-report of physician diagnosis, and approximately 25% of US adults with diabetes have not been identified by a clinician (although we expect this proportion to be smaller in Sweden because of greater access to medical care); if misclassification of diabetes status was non-differential with respect to MD (as indicated by previous work (50)), this would bias our results toward, rather than away from, the null. Despite the reliance on self-reported T2DM, our results are consistent with studies that have used fasting glucose measures to determine diabetes status (6). Although over 95% of cases of diabetes in the adult population are type 2 (51), without additional clinical measures we cannot be certain that all cases investigated here were type 2. Finally, although we leveraged age of onset data, MD and T2DM were assessed at the same time which may have introduced measurement error. Also, because of the substantial correlation between MZ twins for T2DM including the index of genetic risk in the models may have introduced some collinearity; we did not have additional information on family history of diabetes to index genetic risk. Finally, the prevalence of T2DM in our sample was lower than in the US, but is consistent with other nationwide estimates from Sweden (52), which may have limited our ability to detect significant associations. This study also has a number of strengths. The large, population-based sample limits the influence of selection bias and enhances the generalizability of the findings. We were also able to investigate variation in the MD-T2DM relationship by age, sex, and birth weight, all important potential modifiers of this association. Finally, MD was assessed using a validated diagnostic instrument.

Future research should focus on identifying and intervening on modifiable mechanisms that link MD to T2DM. An integrative approach that reflects the dynamic nature of this relationship and which aims to intervene at multiple levels (e.g., individual behaviors, family support, community resources) is likely needed to substantially address the relation between psychiatric and medical conditions in mid-life (2, 42).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acronyms used in text

MD	major depression
T2DM	type 2 diabetes mellitus
SALT	Screening Across the Lifespan Twin
MZ	monozygotic
DZ	dizygotic
CIDI	Composite International Diagnostic Inventory
HPA	hypothalamic-pituitary-adrenal axis

REFERENCES

1. Benton T, Staab J, Evans DL. Medical comorbidity in depressive disorders. *Ann Clin Psychiatry*. 2007; 19(4):289–303. [PubMed: 18058286]
2. Mezuk, B.; Gallo, JJ. Depression and medical illness in late life: Race, resources, and stress. In: Levretsky, H.; Sajatovic, M.; Reynolds, CF., editors. *Depression in Late Life*. New York, NY: Oxford University Press; 2013. p. 270-294.
3. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: A meta-analysis. *Diabetes Care*. 2008; 31(12):2383–2390. [PubMed: 19033418]
4. Coleman SM, Katon W, Lin E, Von Korff M. Depression and death in diabetes: 10-year followup of all-cause and cause-specific mortality in a diabetic cohort. *Psychosomatics*. 2013; 54(5):428–436. [PubMed: 23756124]
5. Van Dooren FE, Neefs G, Schram MT, Verhey FR, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: A systematic review and meta-analysis. *PLoS One*. 2013; 8(3):e57058. [PubMed: 23472075]
6. Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, Lee HB, Lyketsos C. Examining a bidirectional association between depressive symptoms and diabetes. *JAMA*. 2008; 299(23):2751–2759. [PubMed: 18560002]
7. Rubin RR, Ma Y, Marrero DG, Peyrot M, Barrett-Connor EL, Kahn SE, Haffner SM, Price DW, Knowler WC. Diabetes Prevention Program Research Group. Elevated depression symptoms, antidepressant medicine use, risk of developing diabetes during the diabetes prevention program. *Diabetes Care*. 2008; 31(3):420–426. [PubMed: 18071002]
8. Bhattacharjee S, Bhattacharya R, Kelley GA, Sambamoorthi U. Antidepressant use and new onset diabetes: A systematic review and meta-analysis. *Diabetes Metab Res Rev*. 2013; 29(4):273–284. [PubMed: 23390036]
9. Pan A, Sun Q, Okereke OI, Rexrode KM, Rubin RR, Lucas M, Willett WC, Manson JE, Hu FB. Use of antidepressant medication and risk of type 2 diabetes: results from three cohorts of US adults. *Diabetologia* Jan. 2012; 55(1):63–72.
10. Barnard K, Peveler RC, Holt RIG. Antidepressant Medication as a Risk Factor for Type 2 Diabetes and Impaired Glucose Regulation: Systematic Review. *Diabetes Care*. 2013; 36(10):3337–3324. [PubMed: 24065841]
11. Neale MC, Kendler KS. Models of comorbidity for multifactorial disorders. *Am J Human Genetics*. 1995; 57(4):935–953. [PubMed: 7573055]
12. Kendler KS, Gatz M, Gardner CO, Pedersen NL. A Swedish national twin study of lifetime major depression. *Am J Psychiatry*. 2006; 163(1):109–114. [PubMed: 16390897]
13. Almgren P, Lehtovirta M, Isomaa B, Sarelin L, Taskinen MR, Lyssenko V, Tuomi T, Groop L. Botnia Study Group. Heritability and familiarity of type 2 diabetes and related quantitative traits in the Botnia Study. *Diabetologia*. 2011; 54(11):2811–2819. [PubMed: 21826484]

14. Poulsen P, Kyvik KO, Vaag A, Beck-Neilsen H. Heritability of type II diabetes mellitus and abnormal glucose tolerance: A population-based twin study. *Diabetologia*. 1999; 42(2):136–145.
15. Kendler KS, Gatz M, Gardner CO, Pedersen NL. Age at onset and familial risk for major depression in a Swedish national twin sample. *Psychol Med*. 2005; 35(11):1573–1579. [PubMed: 16219115]
16. Kendler KS, Gardner CO, Fiske A, Gatz M. Major depression and coronary artery disease in the Swedish twin registry: phenotypic, genetic, and environmental sources of comorbidity. *Arch Gen Psychiatry*. 2009; 66(8):857–863. [PubMed: 19652125]
17. Xian H, Scherrer JF, Franz CE, McCaffery J, Stein PK, Lyons MJ, Jacobsen K, Eisen SA, Kremen WS. Genetic vulnerability and phenotypic expression of depression and risk for ischemic heart disease in the Vietnam Era Twin Study of Aging. *Psychosom Med*. 2010; 72(4):370–375. [PubMed: 20190130]
18. McCaffery JM, Niaura R, Todaro JF, Swan GE, Carmelli D. Depressive symptoms and metabolic risk in adult male twins enrolled in the National Heart, Lung, and Blood Institute Twin Study. *Psychosom Med*. 2003; 65(3):490–497. [PubMed: 12764224]
19. Scherrer JF, Xian H, Lustman PJ, Franz CE, McCaffery J, Lyons MJ, Jacobson KC, Kremen WS. A test for common genetic and environmental vulnerability to depression and diabetes. *Twin Res Hum Genet*. 2011; 14(2):169–172. [PubMed: 21425899]
20. Pedersen NL, Lichtenstein P, Svedberg P. The Swedish Twin Registry in the third millennium. *Twin Res Hum Genet*. 2002; 5(5):427–432.
21. Lichtenstein P, de Faire U, Floderus B, Svartengren M, Svedberg P, Pedersen NL. The Swedish Twin Registry: A unique resource for clinical, epidemiological and genetic studies. *J Intern Med*. 2002; 252(3):184–205. [PubMed: 12270000]
22. Kessler RC, Andrews G, Mroczek D, Ustun TB, Wittchen HU. The World Health Organization Composite International Diagnostic Interview Short Form (CIDI-SF). *Int J Meth Psych Res*. 1998; 7:171–185.
23. Eaton WW, Hall AL, MacDonald R, McKibben J. Case identification in psychiatric epidemiology: A review. *Int Rev Psychiatry*. 2007; 19(5):497–507. [PubMed: 17896230]
24. Thompson C, Syddall H, Rodin I, Osmond C, Barker DJ. Birth weight and risk of depressive disorder in late life. *Br J Psychiatry*. 2001; 179:450–455. [PubMed: 11689404]
25. Li Y, Qi Q, Workalemahu T, Hu FB, Qi L. Birth weight, genetic susceptibility and adulthood risk of type 2 diabetes. *Diabetes Care*. 2012; 35(12):2479–2484. [PubMed: 22923665]
26. Neale MC, Cardon LR. *Methodology for genetic studies of twins and families*. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1992.
27. Heath AC, Kessler RC, Neale MC, Hewitt JK, Eaves LJ, Kendler KS. Testing hypotheses about direction of causation using cross-sectional family data. *Behav Genet*. 1993; 23(1):29–50. [PubMed: 8476389]
28. Boker SM, Neale MC, Maes HH, Wilde M, Spiegel M, Brick T, Spies J, Estabrook R, Kenny S, Bates T, Mehta P, Fox J. *OpenMx: An Open Source Extended Structural Equation Modeling Framework*. *Psychometrika*. 2011; 76(2):306–317. [PubMed: 23258944]
29. Boker SM, Neale MC, Maes HH, Wilde MJ, Spiegel M, Brick TR, Estabrook R, Bates TC, Mehta P, von Oertzen T, Gore RJ, Hunter MD, Hacket DC, Karch J, Brandmaier A. *OpenMx 1.3 User Guide*. 2012
30. Marmot M. Social Determinants of Health Inequalities. *Lancet*. 2005; 365(9464):1099–1104. [PubMed: 15781105]
31. Kessler RC. The effects of stressful life events on depression. *Ann Rev Psych*. 1997; 48:191–214.
32. Miller GE, Rohleder N, Cole SW. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. *Psychosom Med*. 2009; 71(1):57–62. [PubMed: 19073750]
33. Dallman MF. Stress-induced Obesity and the Emotional Nervous System. *Trends Endocrinol Metab*. 2010; 21(3):159–165. [PubMed: 19926299]
34. Chida Y, Hamer M. Association of adverse psychosocial factors with diabetes mellitus: A meta-analytic review of longitudinal cohort studies. *Diabetologia*. 2008; 51(12):2168–2178. [PubMed: 18806995]

35. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, Blackett KN, Sittih-amorn C, Sato H, Yusuf S. INTERHEART investigators. Association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries. *Lancet*. 2004; 364(9438):953–962. [PubMed: 15364186]
36. McEwen BS, Gianaros PJ. Central role of the brain in stress and adaptation: links to socioeconomic status, health and disease. *Ann NY Acad Sci*. 2010; 1186:190–222. [PubMed: 20201874]
37. Jackson JS, Knight KM, Rafferty JA. Race and unhealthy behaviors: chronic stress, the HPA Axis, and physical and mental health disparities over the life-course. *Am J Public Health*. 2010; 100(5): 933–939. [PubMed: 19846689]
38. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a qualitative summary of four decades of research. *Psychosom Med*. 2011; 73(2):114–126. [PubMed: 21257974]
39. Lucas M, Chocano-Bedoya P, Shulze MB, Mirzaei F, O'Reilly ÉJ, Okereke OI, Hu FB, Willett WC, Ascherio A. Inflammatory dietary pattern and risk of depression among women. *Brain Behav Immun*. 2014; 36:46–53. [PubMed: 24095894]
40. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry*. 2013; 18(6):692–699. [PubMed: 23089630]
41. Rosmond R, Bjorntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes, and stroke. *J Intern Med*. 2000; 247(2):188–197. [PubMed: 10692081]
42. Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Ann Rev Clin Psych*. 2009; 5:363–389.
43. Nouwen A, Nefs G, Carmlau I, Connock M, Winkley K, Lloyd CE, Peyrot M, Pouwer F. European Depression in Diabetes Research Consortium. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. *Diabetes Care*. 2011; 34(3): 752–762. [PubMed: 21357362]
44. Mezuk B, Johnson-Lawrence V, Lee H, Rafferty JA, Abdou CM, Uzogara EE, Jackson JS. Is ignorance bliss? Depression, antidepressants and the diagnosis of pre-diabetes and type 2 diabetes. *Health Psych*. 2013; 32(3):254–263.
45. Nicolucci A, Kavas Burns K, Holt RI, Comaschi M, Hermanns N, Ishii H, Kokoszka A, Pouwer F, Skovlund SE, Stuckey H, Tarkun I, Vallis M, Wens J, Peyrot M. Diabetes attitudes, wishes and needs second study (DAWN2): Cross-national benchmarking of diabetes-related psychosocial outcomes for people with diabetes. *Diabetic Med*. 2013; 30(7):767–777. [PubMed: 23711019]
46. Takayanagi Y, Spira AP, Roth KB, Gallo JJ, Eaton WW, Mojtabai R. Accuracy of reports of lifetime mental and physical disorders: results from the Baltimore epidemiological catchment area study. *JAMA Psychiatry*. 2014; 71(3):273–280. [PubMed: 24402003]
47. Demakakos P, Zaninotto P, Nouwen A. Is the association between depressive symptoms and glucose metabolism bidirectional? Evidence from the English Longitudinal Study of Ageing. *Psychosom Med*. 2014; 76(7):555–561. [PubMed: 25077428]
48. Zhang X, Norris SL, Gregg EW, Cheng YJ, Beckles G, Kahn HS. Depressive symptoms and mortality among persons with and without diabetes. *Am J Epidemiol*. 2005; 161(7):652–660. [PubMed: 15781954]
49. Coleman SW, Katon W, Lin E, Von Korff M. Depression and death in diabetes: 10-year follow-up of all-cause and cause-specific mortality in a diabetic cohort. *Psychosomatics*. 2013; 54(5):428–436. [PubMed: 23756124]
50. Mezuk B1, Eaton WW, Golden SH, Ding Y. The influence of educational attainment on depression and risk of type 2 diabetes. *Am J Public Health*. 2008; 98(8):1480–1485. [PubMed: 18556604]
51. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2013; 36(Suppl 1):S67–S74. [PubMed: 23264425]
52. Organisation for Economic Co-operation and Development (OECD). Diabetes prevalence and incidence. OECD Publishing; 2012. Health at a glance: Europe 2012. Section 1.14. Available at: <http://dx.doi.org/10.1787/9789264183896-en>

Panel A: MD predicting T2DM

Panel B: T2DM predicting MD

Figure 1.

Kaplan-Meier plots of major depression predicting T2DM (panel A) and T2DM predicting major depression (panel B) for twins aged 40 – 55 years old.

Figure 2.
Cholesky decomposition of major depression and type 2 diabetes, twins aged 40 – 55 years.
Illustration of best-fitting bivariate twin model. Values are unstandardized path coefficients.
Model AIC: -24788.15.

Table 1

Characteristics of the Screening Across the Lifespan Twin Study

Participant characteristics	N (%)
Total N	37,043
Twin type	
MZ	8455 (22.8%)
Female – Female	3840 (10.4%)
Male – Male	2884 (7.8%)
Female with missing pair	900 (2.4%)
Male with missing pair	831 (2.2%)
DZ	28588 (77.2%)
Female – Female	5472 (14.8%)
Male – Male	4188 (11.3%)
Female – Male	11144 (30.1%)
Female with missing pair	4302 (11.6%)
Male with missing pair	3482 (9.4%)
Age (Mean, SD)	58.97 (10.88)
Age 40 – 55 years	16631 (44.9%)
Age 56+ years	20412 (55.1%)
Birth weight (M, SD)	2541.4 (671.0)
Very low birth weight (<1500g)	635 (1.7%)
Low birth weight (1500 to <2500g)	6958 (18.8%)
Normal birth weight (≥2500g)	9382 (25.3%)
Current smoker (N, %)	9389 (25.4%)
Generalized anxiety disorder (N, %)	352 (1.0%)
<i>Main variables</i>	
Type 2 diabetes	1733 (4.7%)
Age of type 2 diabetes onset (Mean, SD)	57.34 (12.6)
Major depression	7172 (19.4%)
Age of major depression onset (Mean, SD)	40.63 (12.2)

Restricted to SALT participants with complete data on age, sex, and zygosity. N=16,973 for birth weight.

Table 2
Odds ratio and tetrachoric correlation coefficients for MD and T2DM by age group and sex

	Odds ratio	Male MZ pairs p (SE)	Male DZ pairs p (SE)	Female MZ pairs p (SE)	Female DZ pairs p (SE)
Aged 40 to 55					
MD	--	0.22 (0.08)	0.12 (0.07)	0.48 (0.05)	0.21 (0.05)
T2DM	1.40 (1.10, 1.78)	0.84 (0.07)	0.27 (0.17)	0.83 (0.09)	0.40 (0.22)
MD-T2DM		0.11 (0.09)	0.03 (0.08)	0.21 (0.10)	0.32 (0.08)
N pairs		706	991	919	1264
Aged >55					
MD	--	0.41 (0.09)	0.16 (0.08)	0.43 (0.05)	0.11 (0.05)
T2DM	1.00 (0.86, 1.16)	0.80 (0.05)	0.32 (0.08)	0.71 (0.06)	0.39 (0.08)
MD-T2DM		-0.06 (0.08)	-0.06 (0.06)	-0.04 (0.06)	-0.01 (0.04)
N pairs		740	1106	1005	1474

Odds ratio adjusted for age.

N refers to the number of twin pairs with complete data on both MD and T2DM.

Table 3

Cox Proportional Hazards Model of the Bi-Directional Association of MD and T2DM

	<u>Age 40 – 55</u>		<u>Age >55</u>	
	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
MD predicting T2DM				
MD (<i>ref. Never</i>)	1.49 (1.14 – 1.94)	1.32 (1.00 – 1.80)	1.04 (0.89 – 1.21)	1.00 (0.83 – 1.21)
T2DM predicting MD				
T2DM (<i>ref. Never</i>)	1.40 (1.12 – 1.74)	1.33 (1.02 – 1.72)	1.05 (0.91 – 1.22)	1.02 (0.85 – 1.22)
N	16631	16631	20214	20214

HR: Hazard ratio from Cox proportional hazards model.

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, and genetic risk as indexed by co-twin status.

Table 4

Comparison of the fit of competing twin models of the nature of the MD-T2DM relationship: Age 40 – 55

Model description	Log-likelihood	AIC	Degrees of freedom difference vs. Bivariate ACE	P value
Full Bivariate ACE (Non-causal: MD-T2DM due to shared genetic and/or environmental factors)	4626.04	–10135.96	--	--
Bidirectional causation (MD ↔ T2DM)	4623.16	–10140.85	1	0.99
Unidirectional causation (MD → T2DM)	4626.49	–10139.51	2	0.80
Unidirectional causation (T2DM → MD)	4630.00	–10136.00	2	0.14
No correlation between MD and T2DM	4636.43	–10131.57	3	0.024

P-value from –2Log-likelihood test of relative model fit. Limited to twins aged 40 – 55.