ORIGINAL ARTICLE

OPEN

Genetic Overlap Between Type 2 Diabetes and Depression in a Sri Lankan Population Twin Sample

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ABSTRACT

Objective: Results from twin studies examining the genetic overlap between type 2 diabetes and depression are currently inconclusive. This question has not been addressed in non-Western populations. We aimed to examine whether there are common genetic factors between type 2 diabetes and depression in a Sri Lankan population using genetic model-fitting analysis.

Method: The Colombo Twin and Singleton Study–Phase 2 consists of 2019 singletons, and 842 monozygotic and 578 dizygotic twin pairs. The primary outcomes were self-reported type 2 diabetes diagnosis and Beck Depression Inventory scores. Standard bivariate twin models were fitted to estimate the genetic and environmental (co)variance of type 2 diabetes and depression.

Results: In the best-fitting model, the phenotypic correlation between type 2 diabetes and depression was significant in female individuals only (r = 0.15 [0.08–0.21]). This association was primarily attributed to a significant genetic correlation between the traits (rA = 0.53 [0.19–0.98]).

Conclusions: In female individuals, but not male individuals, we found a significant genetic overlap between type 2 diabetes and depression in the context of a modest phenotypic correlation.

Key words: type 2 diabetes, depression, genetic, twin, structural equation modeling.

INTRODUCTION

Type 2 diabetes (T2DM) and depression are common disorders with considerable impact at personal, societal, and national levels. An association between T2DM and depression is well documented in epidemiological studies, with up to 60% increased risk for developing T2DM in individuals with depression and 15% for incident depression in those with T2DM alone (1,2). Depression is significantly associated with suboptimal glycemic control, higher complication rates, and increased mortality in people with T2DM (3–5). In addition, systemic inflammation, hypercortisolism, and disturbed immune functions have been demonstrated to contribute to the T2DM-depression association (6–8). Similar neuroimaging changes in white and gray matters have been observed in both people with T2DM and depression (9). There is now increasing evidence for common biological mechanisms being at play in the causal pathway for both T2DM and depression (10). It is therefore plausible that genetic pleiotropy between T2DM and depression might also explain some of the comorbidity observed. Furthering our understanding of the underlying mechanism of the T2DM-depression association will allow us to develop treatments and improve outcomes in this high-risk comorbid group.

Four twin studies have examined the genetic overlap between T2DM and depression. Two studies reported no evidence of correlated genetic factors (11,12), whereas qualitative and quantitative sex differences were reported in the (genetic) association of T2DM and depression in two large Scandinavian populations (13). Two studies using a polygenic score approach (14,15) and two studies using a linkage disequilibrium score approach (16,17) in genome-wide association studies (GWAS) have, however, reported no evidence of a genetic overlap between T2DM and depression. These studies were conducted in Western populations. The only non-Western population

AIC = Akaike information criterion, **HbA_{1c}** = glycated hemoglobin, **GWAS** = genome-wide association studies, **T2DM** = type 2 diabetes

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Received for publication March 27, 2019; revision received August 16, 2019.

DOI: 10.1097/PSY.0000000000000771

study examining this association from a genetic perspective was conducted collectively in six ethnic groups, namely, East Asian, South Asian, European, African, Latin American, and Native North American (14). Although the association between T2DM and depression has been observed in non-Western populations (18–20), its genetic determinants have yet to be examined and there are reasons to suggest that these might be different. In addition, the point prevalence of depression has been reported to vary with the human development index (21), whereas the prevalence of T2DM in non-Western populations is rapidly increasing, with a younger age of onset and greater mortality, in comparison with Western populations (22). Furthermore, previous twin studies have raised the possibility that the genetic architecture of depression might be different in non-Western populations, especially in male individuals (23). To further complicate the picture, epidemiological studies in Western populations have reported a substantially higher prevalence rate of comorbid T2DM and depression in female compared with male individuals (24–26). A genetic model incorporating possible quantitative and qualitative sex differences in genetic and environmental effects is therefore called for. In this study, we aimed to examine the genetic overlap of T2DM and depression in a South-Asian (Sri Lankan) twin population sample using sex-limitation genetic model-fitting analysis.

METHODS

Sample

The Colombo Twin and Singleton Study (CoTaSS) is a population-based sample of twins and a comparable sample of nontwins (singletons) born in the Colombo district of Sri Lanka, with >90% participation rate (23). CoTaSS-2 is a follow-up of the original study and was conducted between 2012 and 2014, with a >75% participation rate (83% in twins, 62% singletons) (27). In brief, CoTaSS-2 was designed to examine the relationship between metabolic risk factors and mental health. Written informed consent was obtained from all participants. Demographic and phenotypic data were collected through extensive health care questionnaires, whereas anthropometric and biological data were collected by trained research assistants. The study received ethical approval from the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee at King's College London (United Kingdom; reference number: PNM/10/11-124) and the Faculty of Medical Sciences Ethical Review Committee at the University of Sri Jayewardenepura (Sri Lanka; reference number: 596/11).

Outcome Variables

T2DM was defined as the presence of T2DM as reported by the participants. In addition, fasting blood glucose and glycated hemoglobin (HbA_{1c}) levels were collected 8 months after participants were recruited into the study. Depression was measured using the Beck Depression Inventory (BDI), which captures depressive symptoms and severity in the past 2 weeks (28). The BDI was translated into Sinhalese by a panel of clinical professionals fluent in both Sinhalese and English. The BDI questionnaire was cross-culturally adapted in wording to best describe the questions in their meaning (29) and has been previously been validated in the Sri Lankan population (23). Secondary variables included self-reported age and sex. Zygosity of same-sex twin pairs was based on a standard self-report questionnaire measure of similarity (30).

Statistical Analysis

The classical twin method builds on the following three main assumptions: (i) monozygotic (MZ) twins share 100% and dizygotic (DZ) twins share on average 50% of their segregating genes (additive genetic effects); (ii) MZ and DZ twins are correlated for environmental influences to the same extent (equal environment assumption); and (iii) mating in the population occurs at random (nonassortative mating). In a univariate ACE model, individual differences in a trait are assumed to arise from additive genetic (A), common environmental (C), and unique environmental (E) influences. In a bivariate ACE model, in addition to the A, C, and E components of each trait, the phenotypic correlation between two traits can be partitioned into correlating addictive genetic (rA), shared environmental (rC), and unique environmental (rE) effects (31). Having same-sex male and female MZ and DZ twin pairs as well as opposite-sex twin pairs allows for testing for (i) "qualitative sex differences" where different genetic and common environmental factors are involved in male and female individuals, and (ii) "quantitative sex differences" where the same genetic and environmental factors are involved, but the magnitude of their effect is modulated by sex. The power to estimate qualitative sex differences is based on differences of within-trait and cross-trait correlations in opposite-sex DZ pairs compared with same-sex DZ pairs, whereas the power to estimate quantitative sex differences is based on differential MZ and DZ within-trait and cross-trait correlations in same-sex twin pairs.

A full sex-limitation model was first fitted in which the A, C, and E parameters were allowed to differ between male and female individuals, allowing to test for quantitative sex differences. In addition, for opposite-sex pairs, the correlations between the A factors and the C factors between male and female individuals were estimated freely in succession. These two models were then compared with the model in which the correlations between the A factors were constrained to 0.5 and those between the C factors to 1 in opposite-sex pairs, respectively. This allows us to test for qualitative sex differences. Equating the male and female parameters allows us to test for quantitative sex differences. The software program OpenMx (32) was used for genetic model-fitting analysis on combined dichotomous T2DM data and continuous, log-transformed sex- and age-regressed BDI residual scores. Age effects on T2DM were modeled on the liability threshold.

Two criteria were used to choose the best-fitting model: (i) differences in minus twice the log likelihood (−2LL) distributed as χ^2 and (ii) Akaike information criterion (AIC) (33), with lower values indicating a better balance between explanatory power and parsimony and a difference in AIC of ≥10 indicating substantial support in favor of the more parsimonious model.

RESULTS

Descriptive Statistics

The CoTASS-2 sample used in this analysis consisted of 3956 twin individuals (1963 twin pairs and 30 twin individuals) and 2019 singletons. Of the twin individuals, 42.8% was MZ, 29.8% was same-sex DZ, and 27.4% was opposite-sex DZ (Table 1). The mean (SD) age was 43.0 (14.3) years, and mean (SD) body mass index was 23.8 (4.6) kg/m^2. There were 471 cases with self-reported T2DM in total. For the entire sample, the mean (SD) fasting plasma glucose was 6.0 (2.3) mmol/L. The mean (SD) HbA_{1c} was 42.1 (15.3) mmol/mol as per International Federation of Clinical Chemistry (IFCC) units and 6.0% (1.4%) as per Diabetes Control and Complications Trial (DCTT) units. The intra-assay and interassay coefficients of variations for HbA_{1c} were 0.6 and 2.66 from set 1 and 0.32 and 2.61 from set 2, respectively. For individuals with a self-reported diagnosis of T2DM, the mean (SD) fasting plasma glucose was 8.9 (4.3) mmol, and mean (SD) HbA_{1c} values were 3.8 (47.0) mmol/mol) as per IFCC and 8.9% (4.3%) as per DCTT. For individuals who did not report a diagnosis of T2DM, the mean (SD) fasting plasma glucose was 5.6 (1.4) mmol/L, and mean HbA_{1c} was 38.8 (9.8) mmol/mol as per IFCC and 5.7% (0.9%) as per DCTT.

The recommended diagnostic cutoff values for T2DM using HbA_{1c} are ≥48 mmol/mol as per IFCC and 6.5% as per DCTT,

TABLE 1. Descriptive Statistics of Monozygotic and Dizygotic Twins, Stratified by Sex

	Male	Female
No. paired twins/no. single twins		
MZ	368/4	474/4
DZ	268/7	310/14
Opposite sex	543/1	
Age, mean (SD), y		
MZ	38.2 (12.3)	39.7 (12.7)
DZ	40.0 (12.8)	43.0 (14.0)
Opposite sex	40.7 (13.0)	
BMI, mean (SD), kg/m^2		
MZ	22.9 (4.3)	23.8 (4.6)
DZ	22.7 (4.0)	24.3 (4.7)
Opposite sex	23.7 (4.6)	
No. T2DM cases		
MZ	40	51
DZ	32	61
Opposite sex	82	
Fasting plasma glucose, mean (SD), mmol/L		
MZ	5.6 (1.6)	5.8 (2.5)
DZ	5.8 (1.7)	6.1 (2.7)
Opposite sex	5.9 (2.1)	
HbA_{1c}, IFCC (mmol/mol)/DCTT (%), mean (SD)		
MZ	39.9 (12.0)/5.8 (1.1)	41.0 (15.3)/5.9 (1.4)
DZ	39.9 (14.2)/5.8 (1.3)	42.1 (16.4)/6.0 (1.5)
Opposite sex	41.0 (14.2)/5.9 (1.3)	
Beck Depression Inventory, mean (SD)		
MZ	3.7 (5.2)	4.6 (5.7)
DZ	3.8 (5.5)	5.1 (6.1)
Opposite sex	4.6 (6.1)	
Probandwise concordance rate for T2DM/no. concordant pair, no. discordant pair		
MZ	0.69/11, 10	0.48/10, 22
DZ	0.24/3, 19	0.26/6, 35
Opposite sex	0.25/8, 49	

MZ = monozygotic twins; DZ = dizygotic twins; BMI = body mass index; T2DM = type 2 diabetes; HbA_{1c} = glycated hemoglobin; IFCC = International Federation of Clinical Chemistry units; DCTT = Diabetes Control and Complications Trial units.

and for fasting plasma glucose, the value is ≥7.0 mmol/L (34). Among individuals with self-reported T2DM and for whom biological samples were available (n = 426), 320 (75.1%) had either HbA_{1c} or fasting plasma glucose, or both, above diagnostic cutoffs (Figure 1). Both HbA_{1c} and fasting plasma glucose can be within the reference range among people with well-controlled T2DM and therefore do not exclude T2DM being present. Among individuals who did not report having a T2DM diagnosis and for whom biological samples were available (n = 2966), 244 (8.2%) had either HbA_{1c} or fasting plasma glucose, or both, above diagnostic cutoffs (Figure 1). This suggests that there might be a small proportion of individuals in CoTaSS-2 who fulfill the diagnostic criteria for T2DM but are unaware of the disease process.

The mean (SD) BDI depression score was 4.9 (6.2; Cronbach α = .87), with 355 individuals (9.2%) scoring higher than 13, the cutoff for a clinical diagnosis of depression using the BDI. The BDI scores were positively skewed on visual inspection, with a kurtosis of 6.98, which reduced to −0.17 after log transformation of the age- and sex-regressed scores. In male individuals, the phenotypic correlations between depression and (i) self-reported T2DM diagnosis, (ii) fasting blood glucose, and (iii) HbA_{1c} were 0.06 (95% confidence interval = −0.02 to 0.14), 0.06 (0–0.11), and 0.06 (0.01–0.11), respectively. In female individuals, they were 0.15 (0.08–0.21), 0.05 (0.01–0.10), and 0.06 (0.01–0.10). Correlations stratified by zygosity and sex are summarized in Table 2. Given the small phenotypic correlation between depression and both fasting blood glucose and HbA_{1c}, we focused on the genetic model-fitting between depression and self-reported diagnosis of T2DM.

Genetic Model Fitting

First, a sex-limitation ACE model including quantitative and qualitative genetic sex differences was fitted (HetACEg: −2LL = 15,429.91; df = 7799; AIC = −168.09). Significance of qualitative genetic sex differences was tested by comparing this model with the one in which the correlation between the A and C factors across male and female individuals in opposite-sex pairs were constrained to correlate at 0.50 and 1, respectively, as is the case in same-sex DZ pairs (HetACE: −2LL = 15,432.42; df = 7803; AIC = −174.58). This resulted in a nonsignificant decline in model-fit (HetACEg versus HetACE: $\chi^2_{(df=4)} = 1.52$; p = .82), indicating that qualitative sex differences for the genetic factors were negligible. Second, a sex-limitation ACE model including quantitative and qualitative common environmental sex differences was fitted (HetACEc: −2LL = 15,431.33; df = 7799; AIC = −166.67). Compared with the HetACE model, this model also showed a nonsignificant decline in fit (HetACEc versus HetACE: $\chi^2_{(df=4)} = 0.097$; $p > .99$). Third, we tested for quantitative sex differences by equating the A, C, and E parameters across male and female individuals (HomoACE: −2LL = 15,583.57; df = 7812; AIC = −40.43). Compared with the HetACE model, this resulted in a significant decline in fit (HomoACEc versus HetACE: $\chi^2_{(df=9)} = 152.15$; $p < .0001$), indicating some importance of quantitative sex differences. The best-fitting sex-limitation model with quantitative sex differences only is represented in Figure 2.

Estimates of the standardized additive genetic (heritability; a^2), common (c^2), and unique environment (e^2) variance of the traits were similar across sexes for T2DM: 82% (31%–98%), 12% (0%–61%), and 6% (2%–17%), respectively in male individuals, and 77% (34%–94%), 8% (0%–31%), and 15% (6%–29%), respectively, in female individuals. For depression, the estimates are different across sex for depression: 7% (0%–29%), 22% (6%–36%), and 71% (60%–82%), respectively, in male individuals, and 23% (3%–43%), 13% (0%–31%), and 64% (55%–74%), respectively, in female individuals. The genetic correlation between T2DM and depression was nonsignificant in male individuals (0.38 [−0.21 to 0.84]) but significant in female individuals (0.53 [0.19 to 0.98]). The significant phenotypic correlation in female individuals is mainly due to correlated genetic factors.

DISCUSSION

To our knowledge, this is the first study reporting a significant genetic overlap between T2DM and depression in female individuals in a non-Western population. Our findings in female individuals

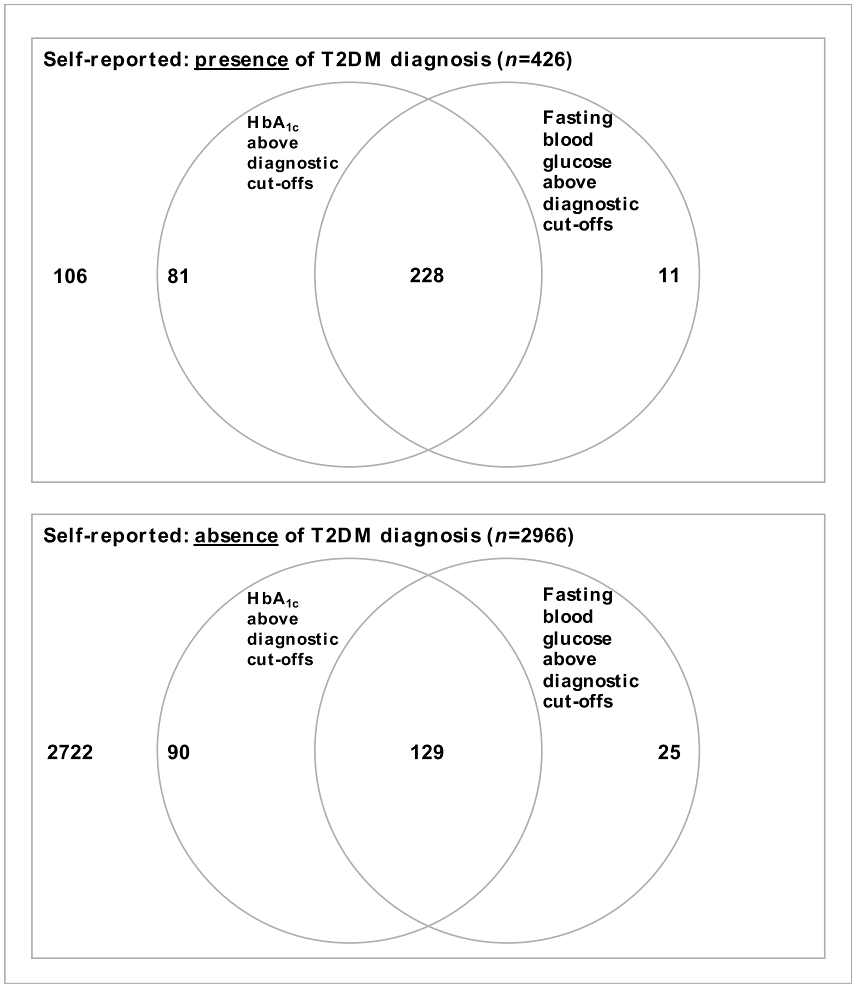

FIGURE 1. Venn diagram of participants with self-reported presence/absence of T2DM and for whom biological samples were available. T2DM = type 2 diabetes; HbA_{1c} = glycated hemoglobin;

TABLE 2. Correlations for (i) T2DM, (ii) Depression, and (iii) T2DM-Depression by Zygosity and Sex

	Male	Female
Within trait (cross twin)		
T2DM		
MZ	0.94 (0.82–0.98)	0.85 (0.70 to 0.94)
DZ	0.44 (−0.03 to 0.76)	0.35 (0.01 to 0.62)
Opposite sex	0.44 (0.16 to 0.65)	
Depression		
MZ	0.29 (0.15 to 0.41)	0.36 (0.25 to 0.45)
DZ	0.24 (0.08 to 0.38)	0.22 (0.07 to 0.34)
Opposite sex	0.12 (0.01 to 0.22)	
Cross trait (cross twin)		
T2DM–depression		
MZ	0.12 (0 to 0.25)	0.21 (0.09 to 0.32)
DZ	0.06 (−0.14 to 0.25)	0.06 (−0.09 to 0.21)
Opposite sex	−0.12 (−0.25 to 0.01)	

T2DM = type 2 diabetes; MZ = monozygotic twins; DZ = dizygotic twins.

are consistent with one previous report in two large Scandinavian populations (13), with most of the phenotypic overlap observed being due to correlated genetic factors. Although the magnitude of our genetic correlation is substantially higher, the wider confidence interval (0.53 [0.19–0.98]) overlaps with estimates derived from the Swedish (0.23 [0.07–0.38]) and Danish (0.18 [0.06–0.31]) twin samples. Our findings differ from two other twin studies that did not report a genetic overlap between T2DM and depression, but the effect of sex was not explored in these two studies (11,12).

The major differences between our findings and previous reports in Western populations are observed for male individuals: first, the phenotypic correlation was nonsignificant for male individuals in our sample (0.06 [−0.02 to 0.14]), whereas it is significant in both the Swedish (male: 0.13 [0.08–0.14], female: 0.16 [0.12–0.17]) and Danish (male: 0.16 [0.12–0.20], female: 0.15 [0.12–0.20]) twin samples. Second, our best-fitting model includes the effects of common environment, whereas previous twin studies do not. This might, in part, be explained by common environmental factors being more important in explaining individual differences in depression for male individuals in non-Western populations like Sri Lanka. The significant effects of common environment factors on depression have been

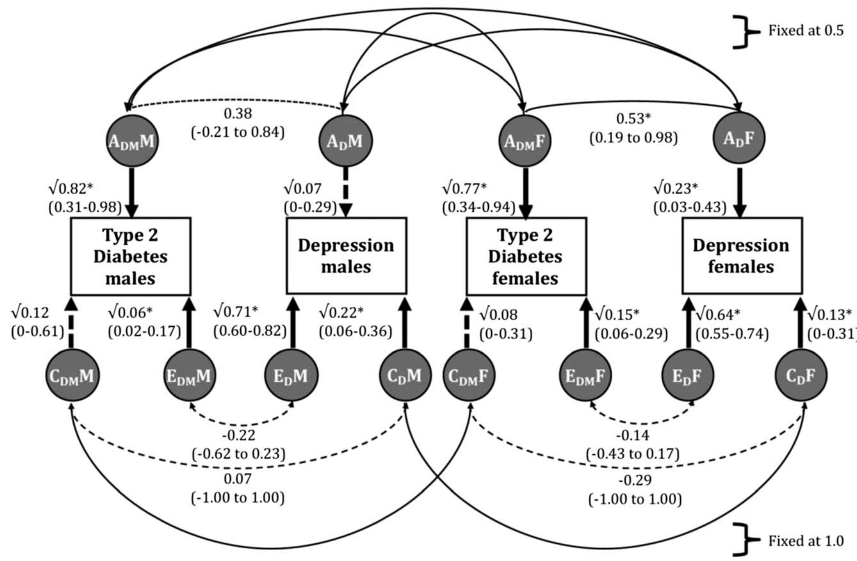

FIGURE 2. Parameter estimates of the bivariate ACE twin model for type 2 diabetes and depression. The diagram above is for best-fit sex-limitation bivariate ACE model for opposite-sex twin pairs. Factor notation: A indicates addictive genetic effects; C common environmental effects; and E unique environmental effects; subscript DM indicates type 2 diabetes and D indicates depression; M stands for male and F for female. Asterisks indicate a significant pathway.

previously reported in a Korean twin sample of adolescents and young adult men (32%, male) (23).

Our heritability estimates for depression in males were also significantly lower than those reported in a meta-analysis (~37%) (35). A possible explanation is that there is more room for environmental factors to explain individual differences in non-Western populations, leading to a lower heritability estimate. Previous studies in the Sri Lankan population have identified male-specific environmental factors to play a role in depression, namely, unemployment, low levels of standard of living, and living in more heavily urbanized areas (36). Our finding of significant common environmental effects in male individuals might therefore reflect the differential economic and social pressures between the sexes in non-Western populations and between Western and non-Western populations in general, and their subsequent effect on developing depression.

In addition to the explanation above, it is possible that a different phenotype of depression might be captured when a questionnaire developed in a Western context is used in a non-Western population. A previous study using the Composite International Diagnostic Interview has demonstrated that the total number of depressive symptoms and pattern of symptoms endorsed were similar between the Sri Lankan and Western populations (36), suggesting some degrees of phenotypic overlap. A study in the United Kingdom has reported that people of South Asian origin were more likely to disclose somatic rather than psychological symptoms when screening for nonpsychotic psychiatric disorders, although the extent of cultural variation in expressing psychological distress remains unclear and controversial (37). Given that no specific measure of environmental factors was included in our analysis, we are merely speculating on the nature and type of environmental factors that might contribute to the T2DM-depression association in non-Western populations. If our findings are replicated in a larger non-Western population twin sample, future studies could examine whether male-specific environmental factors modulate the etiology of depression and its association with T2DM in non-Western populations. It should, however, be noted that non-Western populations are not a uniform entity, highlighting the need to widen the current evidence base of research in non-Western populations. Study-specific differences also need to be taken into account in interpreting our findings: the CoTaSS-2 sample differs from previous twin studies in the assessment of T2DM and depression (self-report questionnaire/diagnosis versus clinical diagnosis derived from hospital records/registries) and being a younger cohort.

Limitation

A major limitation of the study is the reliance on self-report questionnaires for assessing T2DM and depression. Information on diabetes management was unavailable at the time of analysis, limiting the scope of cross-checking self-reported items. We did explore the use of HbA_{1c} as a proxy marker for T2DM, but the phenotypic correlation with depression was very small in magnitude. HbA_{1c} is a useful clinical biomarker for assessing glycemic status and guiding treatment decisions for people with T2DM. It can, however, be within the reference range among people with well-controlled T2DM. For example, ~25% of individuals with T2DM in our study have an HbA_{1c} level of <48 mmol/mol (6.5%), the recommended cutoff for diagnosing T2DM. HbA_{1c} alone might therefore not be a sufficiently reliable tool for recognizing T2DM, especially during the early stages of the disease. In addition, being diagnosed as having T2DM, and initiating and implementing the associated diabetes self-management might have a greater impact on the development of depression than HbA_{1c} alone, explaining the differential phenotypic correlations between depression and (i) T2DM diagnosis and (ii) HbA_{1c}.

For depression, the BDI captures depressive symptoms for the past 2 weeks and is not aimed to establish a diagnosis of major depressive disorder. The main rationale of selecting BDI as an outcome measure for depression in this study is its high internal consistency in both psychiatric and nonpsychiatric samples, rendering it appropriate for CoTaSS-2, a population-based cohort

(38,39). It has also demonstrated high convergent validity with other rating scales for depression and discriminated reliably between individual with and without depressive symptoms (38,39). Psychiatric disorders remain underrecognized in Sri Lanka. A scarcity of mental health resources and stigma have been identified as major barriers for communities to seek care (40). A recent national survey of self-reported health in Sri Lanka reported that only 23% of individuals reporting to have a mental illness receive any treatment (41). In addition, the self-report nature of a questionnaire can affect its results owing to social desirability and respondent educational attainment (42). Thus, a more comprehensive approach would be to conduct a structured diagnostic interview to screen for mental illnesses in the CoTASS-2 sample, but it is both time- and labor-intensive.

Information on antidepressant was also not available at the time of analysis, and thus, it is possible that individuals who were actively depressed and receiving antidepressant treatment were included in the COTASS-2 sample. This can potentially affect their responses on the BDI. To further complicate the picture, mixed results have previously been reported between the association between antidepressants and glycemic control. For example, a cross-sectional study using a large representative population of US adults without a diagnosis of diabetes (n = 6141) concluded that antidepressant use was not associated with an increased risk for abnormalities in glycemic control or undetected diabetes (43). A longitudinal study in adults who were at high risk for developing T2DM, however, demonstrated that antidepressant use is associated with elevated inflammatory markers and incident T2DM (n = 3187) (44). The association between antidepressants use and T2DM has not been extensively examined in non-Western populations, and thus, the effect of antidepressants on HbA_{1c} remains uncertain in the Sri Lankan population.

Adopting a multi-informant approach, such as using a valid and reliable diagnostic interview for depression or cross-validating our measures with a clinical diagnosis and medication registry, could potentially strengthen our finding. Our study also uses cross-sectional data, and thus, we cannot determine the extent by which individuals later develop depression or T2DM after being recruited into the study. A longitudinal design will allow us to examine changes in genetic and environmental influences in the clinical course of T2DM. Lastly, limitations of the classical twin model apply, namely, the equal environment assumption and the assumption of negligible correlations between the A, C, and E factors (45). In addition, it is important to note that the heritability estimates derived from GWAS using techniques such as genome-wide complex trait analysis and linkage disequilibrium score regression are generally half when compared with twin studies (46). The discrepancy currently remains unclear and can in part be due to GWAS only capturing the effects of single nucleotide polymorphisms with a minor allele frequency of greater than 1%. Genome-wide complex trait analysis also does not include nonadditive interactions, such as gene-gene or gene-environment. At this stage, we have only begun to uncover the complex genetic underpinning of the T2DM-depression association.

CONCLUSIONS

Our study strengthens previous reports of genetic factors playing an important role in the mechanism underlying the T2DM-depression link in female individuals by replicating the finding in a non-Western population and thus demonstrating the generalizability of the finding. The reason for the discrepancy in findings between twin and GWAS studies is currently unclear, and it seems that we have only begun to uncover the complex genetic underpinning of the association between T2DM and depression.

The project is based on data from CoTaSS-2, and the authors would like to thank all participants.

M.H., A.S., and F.R. were involved in funding application and are principal investigators on CoTaSS-2.

All authors were involved in the conception of the study. C.K., K.I., and F.R. designed the protocol for this analysis. C.K. performed the statistical analysis and wrote the manuscript. F.R. supervised the statistical analysis. All authors reviewed/edited the manuscript.

Source of Funding and Conflicts of Interest: This project was supported by the Wellcome Trust (Grant No. 093206/Z/10/Z). C.K., L.A., M.H., K.I., and F.R. are partly funded by the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. M.H. is an NIHR Senior Investigator. C.K. has also previously received salary support from Novo Nordisk UK Research Foundation and Maria Currie Fellowship. No potential conflicts of interest relevant to this study were reported from all authors.

The views expressed are those of the authors and not necessarily those of the Wellcome Trust, the NHS, the NIHR, or the Department of Health. The funders did not have a role in the study design, data collection/analysis/interpretation, or preparation of this manuscript.

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