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Do personality traits moderate the manifestation of type 2 diabetes genetic risk?☆

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ABSTRACT

Objective. To test whether personality traits moderate type 2 diabetes (T2D) genetic risk. *Methods*. Using a large community-dwelling sample ($n = 837$, $M_{age} = 69.59 \pm 0.85$ years, 49% males) we fitted a series of linear regression models predicting glycated haemoglobin (HbA1c) from T2D polygenic risk — aggregation of small individual effects of a large number of single nucleotide polymorphisms (SNPs) — and five personality traits. We tested the main effects of personality traits and their interactions with T2D polygenic risk score, controlling for age and sex. The models in the final set were adjusted for cognitive ability, highest educational qualification, and occupational class. *Results*. Lower levels of openness were associated with heightened levels of HbA1c ($\beta = -0.014$, $p = .032$). There was a significant interaction between T2D polygenic risk score and agreeableness: lower agreeableness was related to a stronger association between T2D polygenic risk and HbA1c ($\beta = -0.08$, $p = .021$). In the model adjusted for cognitive ability, the main effect of openness was not significant ($\beta = -0.08$, $p = .057$). The interaction between agreeableness and T2D polygenic risk was still present after controlling for cognitive ability and socioeconomic status indicators, and the interaction between conscientiousness and polygenic risk score was also significant: lower conscientiousness was associated with a stronger association between T2D polygenic risk and HbA1c levels ($\beta = 0.09$, $p = .04$). *Conclusions*. Personality may be associated with markers of diabetes, and may moderate the expression of its genetic risk.

Introduction

Diabetes mellitus is one of the biggest contemporary disease burdens [1]. It is a major risk factor for health complications, including heart disease and stroke, blindness, kidney and nervous system disease, limb amputations, and increased risk of death [2]. In 2011 there were 366 million people with diabetes worldwide, approximately 90% of whom had type 2 diabetes and this number is expected to rise to 552 million by 2030 [3,4]. Given the personal and social costs associated with diabetes, it is imperative to find ways to identify at-risk individuals early, and to engage them in prevention strategies [4,5].

Behavioural factors such as unhealthy diet and physical inactivity, as well as obesity, older age, insulin resistance, and the metabolic syndrome are all commonly recognized risk factors for type 2 diabetes [6]. In addition to these, genetic risk also contributes to type 2 diabetes development [7]. About 10% of the genetic risk is explained by known common genetic variants [8] with the remainder being attributable to small individual effects of a large number of single nucleotide polymorphisms (SNPs) [9]. These small effects may not be individually detectable by current GWAS studies [9], but they may be aggregated across thousands of SNPs to quantify diabetes genetic risk [10–12]. The manifestation of the genetic risk may be moderated by non-genetic factors. For example, there is evidence that dietary habits may interact with the genetic factors predisposing to type 2 diabetes [13–16]. Psychological factors, including those related to the aforementioned dietary habits and depression, could moderate the expression of diabetes among those who are at high genetic risk.

Mõttus et al. recently found that childhood cognitive ability moderates the relationship between polygenic risk for type 2

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diabetes and late life HbA1c levels: participants at a given level of genetic risk with lower cognitive ability at age 11 years were more likely to have heightened HbA1c levels at age 70 than participants with higher childhood cognitive ability [17]. This behavioural trait by genetic risk interaction offers an insight into potential mechanisms by which psychological characteristics may influence health outcomes.

Besides cognitive abilities, other stable behavioural characteristics such as personality traits described by the Five Factor Model [18,19] have been associated with diabetes in both cross-sectional [20,21] and longitudinal [22] studies. More specifically, in one cross-sectional study, participants with diabetes had lower conscientiousness, agreeableness and openness [20]. In another study, participants with diabetes had higher levels of neuroticism [21]. However, in a longitudinal study, higher levels of neuroticism were associated with lower risk of developing type 2 diabetes [22]. In a pooled analysis of five cohorts, lower conscientiousness was related to higher diabetes incidence and mortality [23]. Furthermore, personality has been shown to influence a wide range of behavioural and physiological diabetes risk factors. For example, higher neuroticism and lower openness are related to obesity, high triglycerides, hypertension, and elevated blood glucose, all of which are components of the metabolic syndrome [24,25]. Along with higher neuroticism and lower openness, higher levels of extraversion have been related to aspects of diabetes-prone lifestyle such as unhealthy dietary habits and low levels of physical activity [26,27]. In addition, lower agreeableness has been associated with higher alcohol intake [28]. It is, then, possible that personality trait may influence diabetes by moderating its genetic risk in a way similar to cognitive abilities as shown by Mõttus et al. [17].

Specifically, we hypothesized that personality traits moderate whether genetically at-risk individuals have higher levels of glycated haemoglobin, a diagnostic tool for diabetes mellitus. This hypothesis is based on the direct and indirect — i.e., via other risk factors, associations between personality traits with diabetes, as well as on the recent study [17] showing that higher cognitive ability is protective among participants who are at high genetic risk for diabetes.

Method

Sample

Participants were community-dwelling members of the Lothian Birth Cohort 1936 (LBC1936) — a follow-up study of the Scottish Mental Survey 1947 (SMS1947). On June 4, 1947, nearly all children born in 1936 and attending school in Scotland ($n = 70{,}805$; 35,809 boys) sat the Moray House test of intelligence. Between the years 2004 and 2007, participants from Edinburgh and the Lothians region were identified through the Community Health Index and media advertisements. Of 3810 identified participants, 3686 were identified to take part in the follow-up study. In total, 2318 responses were received, of which 1226 met the eligibility criteria to take part in the study. The final number of tested LBC1936 participants was 1091 [29]. Participants who dropped out of the study during the follow-up time were, on average, of lower intelligence and poorer health status than those assessed in the follow-up, but these difference were relatively small [29]. Full details on the recruitment and testing procedures are provided elsewhere [30]. Of the initial 1091 LBC1936 members, complete data on age, sex, personality traits, HbA1c, and genetic risk were available for 837 participants ($M_{age} = 69.59 \pm 0.85$ years, 48.7% males). All participants provided written informed consent. Ethical approval was obtained from the Ethics the Multi-Centre Research Ethics Committee for Scotland.

Measures

Personality

Personality was assessed using the 60-item NEO Five-Factor Inventory (NEO-FFI), a valid and reliable instrument designed to assess the five personality domains — neuroticism, extraversion, openness, agreeableness, and conscientiousness — of the Five Factor Model [31]. Approximately 50% of the variance in personality traits can be accounted for by genetic influences [32].

Glycated haemoglobin

Glycated haemoglobin (HbA1c) is typically used as an indicator of long-term blood glucose levels [33] and as a diagnostic criterion for diabetes mellitus [34]. About 75% of the variation in the levels of Hba1c is due to genetic influences [35]. The HbA1c levels were analysed from blood taken during participants' visit to the clinic, and were treated as a continuous variable.

T2D polygenic risk

All participants underwent genome-wide genotyping, conducted by the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Western General Hospital, Edinburgh, UK, using the Illumina Human 610-Quadv1 Chip (Illumina Inc., San Diego, CA, USA). The quality control procedures included checks for gender discrepancies, individual relatedness and non-Caucasian descent, and are fully described elsewhere [36].

The polygenic risk score for type 2 diabetes was calculated for each member of the LBC1936 following a previously published meta-analysis on the association between type 2 diabetes and approximately 121,000 SNPs. The meta-analysis comprised 34,840 participants with type 2 diabetes diagnosis and 114,981 healthy controls [8]. The genetic risk score was estimated by inclusion of all available SNPs ($n = 120{,}991$) based on a meta-analysed by Morris et al. [17]. The meta-analytic effect size of each of the SNPs was transformed into a Z-score and multiplied by the number of copies (0/1/2) of the effect allele carried by the individual. These individual risks across all SNPs were summed to form participants' type 2 diabetes all-inclusive polygenic risk score. The calculations were done using PLINK software [37]. A more detailed description of the scoring procedure is provided elsewhere [38].

Covariates

Age and sex

Sex was coded as 0 for females and 1 for males. Age was treated as a continuous variable.

Cognitive ability

Cognitive ability at age 70 was assessed using the Moray House Test no. 12. The test consisted of a variety of items designed to assess reasoning ability, e.g., word classification, analogies, reasoning, and spatial items [30]. Cognitive ability was treated as a continuous variable.

SES indicators

Highest educational qualification was classified into five categories ranging from 'no qualification' to 'university degree'. Occupational class was assessed on a five-point scale ranging from 'manual labour' to 'professional' [39]. Women who reported lower occupational class than their spouse were classified according to their spouses. Both the highest educational qualification and occupational class were treated as continuous variables.

Analyses

We fit a series of linear regression models predicting HbA1c from its polygenic risk score and five personality traits. Models 1–5 tested the