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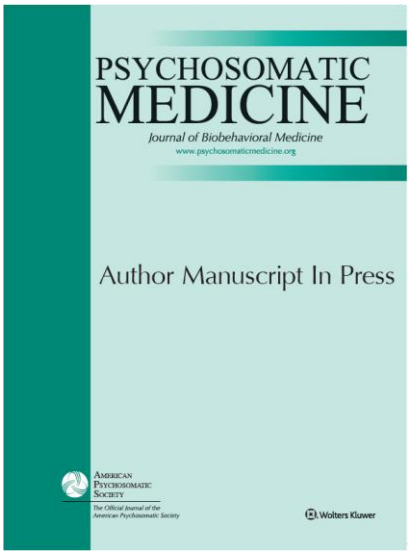
Published in:
Psychosomatic Medicine

DOI:
10.1097/PSY.0000000000000562

Publication date:
2018



Psychosomatic Medicine
Author's Accepted Manuscript

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DOI: 10.1097/PSY.0000000000000562

Received Date: June 21, 2017

Revised Date: Oct 26, 2017

Psychosomatic Medicine Publish Ahead of Print
DOI: 10.1097/PSY.0000000000000562

The interaction of genetic predisposition and socioeconomic position with type 2 diabetes mellitus: cross-sectional and longitudinal analyses from the Lifelines Cohort and Biobank Study

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Conflicts of Interest and Source of Funding: The authors declare no potential conflicts of interest. This project did not receive any specific funding. Authors were funded by their respective institutes.

Abstract

Objective: A strong genetic predisposition for type 2 diabetes mellitus (T2DM) may aggravate the negative effects of low socioeconomic position (SEP) in the etiology of the disorder. This study aimed to examine cross-sectional and longitudinal associations and interactions of a genetic risk score (GRS) and SEP with T2DM, and to investigate whether clinical and behavioral risk factors can explain these associations and interactions.

Methods: We used data from 13,027 genotyped participants from the Lifelines study. The GRS was based on single-nucleotide polymorphisms (SNPs) genome-wide associated with T2DM and was categorized into tertiles. SEP was measured as educational level. T2DM was based on biological markers, recorded medication use, and self-reports. Cross-sectional and longitudinal associations, and interactions, between the GRS and SEP on T2DM were examined.

Results: The combination of a high GRS and low SEP had the strongest association with T2DM in cross-sectional (OR: 3.84; 95% CI: 2.28, 6.46) and longitudinal analyses (HR: 2.71; 1.39, 5.27), compared to a low GRS and high SEP. Interaction between a high GRS and a low SEP was observed in cross-sectional (relative excess risk due to interaction: 1.85; 0.65, 3.05) but not in longitudinal analyses. Clinical and behavioral risk factors mostly explained the observed associations and interactions.

Conclusions: A high GRS combined with a low SEP provides the highest risk for T2DM. These factors also exacerbated each other's impact cross-sectionally but not longitudinally. Preventive

measures should target individual and contextual factors of this high-risk group to reduce the risk of T2DM.

Key words: genetic predisposition, genetic risk score, socioeconomic position, socioeconomic status, type 2 diabetes mellitus, interaction

Abbreviations: ATC – Anatomical therapeutic chemical; BMI – Body mass index; CI – Confidence interval; DPB – Diastolic blood pressure; FPG – Fasting plasma glucose; GRS – Genetic risk score; GWAS – Genome-wide association study; HbA1c – glycated hemoglobin; HR – Hazard ratio; OR – Odds ratio; PC – Principal component score; RERI – Relative excess risk due to interaction; SBP – Systolic blood pressure; SD – Standard deviation; SEP – Socioeconomic position; SNP – Single-nucleotide polymorphism; T2DM – Type 2 diabetes mellitus; WC – Waist circumference

Introduction

Type 2 diabetes mellitus (T2DM) is a common chronic health condition affecting hundreds of millions of people worldwide (1). In 2014, the estimated global prevalence was 9.0% for adult men and 7.9% for adult women (1) T2DM results in a high number of disability adjusted life years, and is a major risk factor for other diseases like cardiovascular disease and chronic kidney disease (2-5) Evidence on T2DM is extensive, but still lacks on the interaction between genetic and environmental factors in the etiology of the disease. This evidence is essential to successfully tackle this major public health problem.

Low socioeconomic position (SEP) is a well-known risk factor for T2DM (6). A systematic review and meta-analysis, including 23 studies with 41 measures of association between low SEP and T2DM incidence, found that low SEP, measured as low educational level, low occupational status, and low income, was associated with increased relative risks for T2DM in high, middle, and low income countries (6) The association between low SEP and T2DM is probably due to a high prevalence of clinical and behavioral risk factors, such as obesity and physical inactivity, among people with a low SEP (7-10) often in co-occurrence (11-13) These risk factors are potentially modifiable.

Genetic and environmental factors have been shown to interact in the etiology of T2DM (14) Regarding SEP and genetic predisposition, one might expect that the negative effects of low SEP on T2DM are aggravated by a strong genetic predisposition through the interplay of genetics and environmental risk factors associated with low SEP (15). This genetic predisposition can be operationalized as a genetic risk score (GRS), which takes into account all

SNPs associated with T2DM (16) If people are not genetically predisposed to the disease i.e. in case of a low GRS, low SEP may have little or no effect.

To our knowledge, only one study investigated the interaction between a GRS and SEP regarding T2DM (15) This study showed that the effect of strong genetic predisposition on HbA1c levels was smaller among people with a higher educational level (15) Studies on specific behavioral and clinical risk factors showed that obesity and a Western dietary pattern (i.e. high intake of red and processed meats and refined foods) interact with genetic predisposition in the etiology of T2DM (17-19) However, evidence lacks on the influence of genetic predisposition on the overarching effect of low SEP in the etiology of T2DM.

The aggravating or buffering effect of a strong or weak genetic predisposition on the effect of low SEP in the etiology of T2DM may also differ by sex, e.g. due to differences in metabolic homeostasis (20)It was previously found that family history of T2DM and low SEP exacerbated each other's impact in females but not in males (21) Because possible sex differences may be important for the design of future prevention and intervention strategies, they need to be taken into account.

Therefore, the main aims of this study are to examine associations and interactions of a GRS and SEP with T2DM, and to investigate whether clinical and behavioral risk factors can explain these associations and interactions. Possible effect modification by sex will be taken into account in the analyses. We will perform cross-sectional and longitudinal analyses to examine both the prevalence and incidence of the disease using data from the Lifelines Cohort and

Biobank Study. We hypothesize that having both a high GRS and a low SEP results in an excess risk for T2DM, and that behavioral and clinical risk factors partly explain this interaction.

Methods

Study design and sample

The study sample was derived from the Lifelines Cohort and Biobank Study (22) Lifelines is a multi-disciplinary prospective population-based cohort study examining the health and health-related behaviors of 167,729 persons living in the north of The Netherlands. Between November 2006 and December 2013, individuals were invited through their general practitioner or a family member, and there was an option for self-registration. The recruitment and collection of data have been described in detail elsewhere (22)

For the present study, we used participants who were genotyped at baseline (n=13,395) on whom phenotypic data were obtained from the baseline measurement, from two follow-up questionnaires after approximately 1.5 and 3 years, and from a physical follow-up measurement after 5 years. The selection and genotyping of this sub-sample has been described in detail elsewhere (23) with the only difference that we used 1000 Genomes imputation instead of HapMap. Lifelines was conducted according to the guidelines in the Declaration of Helsinki and all procedures involving human subjects were approved by the Medical Ethics Committee of the University Medical Center Groningen. Written informed consent was obtained from all participants.

Measures and procedures

Type 2 diabetes mellitus (T2DM)

The presence of T2DM was determined at four measurement points. At baseline, T2DM was diagnosed as having a measured fasting plasma glucose (FPG) ≥7.0 mmol/L (24) and/or a measured HbA1c ≥6.5% (48 mmol/mol) (24) and/or recorded medication use (i.e. anatomical therapeutic chemical (ATC) codes A10A and A10B) (25) and/or self-reported T2DM in combination with self-reported medication use. For the follow-up after 1.5 and 3 years, T2DM diagnosis was based on self-reported new onset of the disease. At the physical follow-up after 5 years, T2DM was diagnosed based on FPG, HbA1c and on self-reported disease. T2DM diagnosis, which does not include type 1 DM cases, and blood value measurements have been described in more detail elsewhere and are in line with previous studies that used Lifelines data (26,27)

Socioeconomic position

Socioeconomic position (SEP) was measured as educational level at baseline. Educational level has been shown to be a good indicator to study socioeconomic health inequalities in the Netherlands (28). In addition, the proportion of missing data is usually small compared to other indicators of SEP (29). Educational level was measured according to the International Standard Classification of Education with a single-item question regarding the highest educational level achieved (30). Educational level was categorized into low (no education, primary education, lower or preparatory vocational education, lower general secondary education), medium (intermediate vocational education or apprenticeship, higher general senior secondary education

or pre-university secondary education), and high SEP (higher vocational education, university), which is the standard categorization of educational level in the Netherlands (31).

Genetic predisposition

To determine participants' genetic predisposition to T2DM, we selected single-nucleotide polymorphisms (SNPs) from the most recent large meta-analysis of genome-wide association studies (GWAS) in European populations (32) supplemented with more recent findings from the same consortium (33-35) Only SNPs with a p-value below the genome-wide significance threshold ($p< 5 \times 10^{-8}$) were included. If two papers reported the same marker, the result with the smallest p-value was selected. Furthermore, we tested for independence by correlating the allele dosages within Lifelines. If the pairwise r^2 value of two SNPs exceeded 0.1, we excluded the SNP with the least significant p-value. For each selected SNP, we collected the alleles, risk-allele frequency, odds ratio (OR) and p-value. See Supplementary Table 1 (Supplemental Digital Content, http://links.lww.com/PSYMED/A441) for the selected SNPs (n=63) and effect sizes.

Participants' genetic predisposition to T2DM was assessed by calculating a weighted genetic risk score (GRS) from ORs obtained from the above mentioned GWAS. First, we log-transformed the ORs to acquire a direct effect-size for each SNP. For each SNP in each participant, we then multiplied the effect-size with the number of risk alleles of that SNP. Adding up these values per participant for all 63 SNPs yields the weighted GRS of that participant. Because there are no clear cut-off points for defining low or high genetic risk, we created three equal groups (i.e. low, medium, or high genetic predisposition for T2DM). This allows for a possible biological gradient without losing too much power.

Behavioral and clinical risk factors

Behavioral and clinical risk factors were measured at baseline and concerned smoking, alcohol consumption, physical activity, body mass index (BMI), waist circumference (WC), and hypertension. *Smoking status* was categorized as being a current smoker, ex-smoker, or never smoker (36) *Alcohol consumption* was categorized into drinking 0 days/week, drinking 0-1 days/week, drinking >1 to 3 days/week and drinking >3 days/week. Because information on the average number of units consumed on a drinking day was not available for half of our study sample (i.e. the question was not included in early versions of the questionnaire), we could not specify alcohol consumption any further. *Physical activity* was based on the number of days per week participants were active for at least half an hour (e.g. bicycle, odd jobs, exercise) and was categorized into being inactive (0-2 days per week), moderately active (3-4 days per week), or active (≥5 day per week). *BMI* was calculated as weight (kg) divided by height (m) squared and used as an index of general weight status. Participants were categorized as having underweight (BMI <18.5), normal weight (BMI ≥18.5 - ≤24.9), overweight (BMI ≥25.0 - ≤29.9) or obesity (BMI ≥30.0) (37) *WC* was measured to the nearest 0.5 centimeter and used as an index for abdominal obesity. Participants were categorized as not having abdominal obesity (WC <102 cm in males, WC <88 cm in females) and having abdominal obesity (WC ≥102 cm in males, WC ≥88 cm in females) (37) *Hypertension* diagnosis was based on measured blood pressure and recorded medication use. A mean systolic and diastolic blood pressure (SBP and DBP, respectively) were measured using an automatic blood pressure monitor (22) Participants with a BP >140/90 mm Hg (38) and participants with recorded antihypertensive medication (i.e. ATC codes C02, C03, C07, C08, C09) (25) were categorized as hypertensive, as was previously done

in Lifelines (26). Clinical measurements were performed by trained research staff using standardized protocols and calibrated measuring equipment (22)

Statistical analyses

First, we created a variable in which we categorized participants into 9 possible groups according to their GRS and SEP. We then described baseline characteristics concerning socio-demographic, behavioral and clinical risk factors. We also calculated the overall baseline prevalence and 5-year incidence of T2DM.

Second, we assessed cross-sectional and longitudinal associations of GRS and SEP with T2DM using logistic regression models and Cox regression models, respectively. Odds ratios (OR) and Hazard ratios (HR) with 95% confidence intervals (CI) were calculated for each category of GRS and SEP, with the reference category being low GRS and high SEP (39) All analyses were adjusted for age, age-squared, sex and the first 10 principal component scores (PCs). Adjusting analyses for the first 10 PCs is common practice to correct for possible population stratification in studies using genotypic data (40) In the longitudinal analysis, we excluded participants with T2DM at baseline. Effect modification of sex was examined by adding an interaction term to the cross-sectional and longitudinal models. Because no effect modification was observed in the cross-sectional ($p = 0.65$) or longitudinal ($p = 0.61$) models, analyses were not stratified by sex.

Third, we assessed the interaction of GRS and SEP regarding T2DM on the additive scale by calculating the relative excess risk due to interaction (RERI), both in cross-sectional and in

longitudinal analyses. The RERI shows whether the risk for T2DM is larger than the sum of the separate risks when both risk factors are present. The additive scale has been shown to best fit the method for assessing biological interaction in previous studies (39,41,42) Analyses were performed using the recommended syntax and Excel tool by Andersson et al (43). To gain further insight, we also examined associations between SEP and T2DM within categories of GRS; and between GRS and T2DM within categories of SEP (39)

Fourth, to examine whether behavioral and clinical risk factors explain the associations and interactions of GRS and SEP with T2DM, we adjusted the basic model stepwise for behavioral and clinical risk factors at baseline. In model 1, we adjusted for smoking status, alcohol consumption, and physical activity. In model 2, we added general weight status and abdominal obesity. In model 3, we included hypertension. Participants with missing data on clinical and behavioral risk factors were excluded from these analyses. In the final cross-sectional and longitudinal models, 13.0% and 11.7% had missing data, respectively. This was mainly due to missing data on physical activity (9.1% and 7.9%), smoking status (4.3% and 4.1%), and alcohol use (2.1% and 1.2%). Data on clinical risk factors was mostly complete (i.e.7 (0.1%) and 6 (0.1%) missing values).

We performed two sensitivity analyses. First, we repeated the second and third step of the analyses using household income instead of educational level as indicator for SEP. Second, we repeated the second and third step of the analyses using quartiles instead of tertiles for the GRS.

Analyses were performed using STATA 13 (Stata Corp, College Station, TX, USA).

Results

Baseline characteristics

In total, 13,027 and 11,756 participants were included in the cross-sectional and longitudinal analyses, respectively (Supplementary Figure 1, Supplemental Digital Content, http://links.lww.com/PSYMED/A441). Baseline characteristics of the cross-sectional study sample are shown by GRS and SEP in Table 1. Participants with a low SEP, regardless of GRS, tended to be older than participants with a medium or high SEP. They were also more often obese, smoker, and had a higher prevalence of hypertension compared to participants with a medium or high SEP. Baseline characteristics of the longitudinal study sample were essentially similar (Supplementary Table 2, Supplemental Digital Content, http://links.lww.com/PSYMED/A441). T2DM prevalence increased with an increasing GRS and decreasing SEP, and was highest for participants with a high GRS and low SEP (8.2%) (Figure 1). T2DM incidence followed a similar pattern but differences between categories were less pronounced. The median follow-up time for the longitudinal study sample was 57.0 months (25^{th} – 75^{th} percentile: 47.0 – 68.0 months). The overall prevalence of T2DM was 3.9% at baseline and the overall incidence during 5-year follow-up was 2.2%. Information about the distribution of the GRS is presented in Supplementary Table 3 and Supplementary Figure 2 (Supplemental Digital Content, http://links.lww.com/PSYMED/A441).

Associations and interactions of GRS and SEP with T2DM

In the cross-sectional analyses, we found statistically significant associations for a high GRS with a low, medium, and high SEP, and for having a medium GRS with medium or low SEP (Table 2). The OR for T2DM was highest for participants with a high GRS and low SEP (OR:

3.84; 95% CI: 2.28, 6.46). We found statistically significant interactions between a high GRS and a low SEP (RERI: 1.85; 95% CI: 0.65, 3.05), and between a medium GRS and a low and medium SEP (Table 2). No interaction was observed between a high GRS and medium SEP.

In the longitudinal analyses, statistically significant associations of GRS and SEP with T2DM were observed for a high GRS with a low or medium SEP, and a medium or low GRS in combination with a low SEP (Table 2). The HR for T2DM was highest for participants with a high GRS and a low SEP (HR: 2.71; 95% CI: 1.39, 5.27). No statistically significant interaction was found between GRS and SEP.

Stratified analyses for T2DM within categories of GRS and SEP

The upper part of Table 3 shows the association of SEP with T2DM within categories of GRS. In the cross-sectional analyses, low and medium SEP were associated with increased odds for T2DM for participants with a medium and high GRS, but not for participants with a low GRS. In the longitudinal analyses, low and medium SEP were associated with T2DM for participants with a high GRS. Moreover, low SEP was associated with T2DM for participants with a low, but not medium, GRS.

The bottom part of Table 3 shows the association of GRS with T2DM within categories of SEP. In the cross-sectional analyses, a high GRS was associated with higher odds for T2DM across all categories of SEP, while a medium GRS was associated with increased odds for T2DM in participants with a medium and low SEP. In the longitudinal analyses, a high or medium GRS were not associated with T2DM within categories of SEP.

The role of clinical and behavioral risk factors in the association and interaction of GRS and SEP with T2DM

Clinical and behavioral risk factors partly explained the associations and interactions of GRS and SEP with T2DM in the cross-sectional analyses (Table 4). After their inclusion, a high GRS was still associated with T2DM across all categories of SEP. A statistically significant interaction between a high GRS and a low SEP was still observed after adjustment for smoking status, alcohol consumption, and physical activity (RERI: 1.20; 95% CI: 0.07, 2.32) (Model 1) but no longer after additional adjustment for weight status (model 2). In the longitudinal analyses, only a high GRS for participants with a medium SEP was still associated with T2DM after adjustment for all clinical and behavioral risk factors (HR: 2.37; 95% CI: 1.13, 4.97) (model 3).

Sensitivity analyses

The first sensitivity analysis showed that associations between SEP and T2DM were somewhat stronger when using household income as indicator for SEP (Supplementary Table 4, Supplemental Digital Content, http://links.lww.com/PSYMED/A441). However, the interaction effect was smaller. The second sensitivity analysis showed that categorizing the GRS into quartiles yields very similar results (Supplementary Table 5, Supplemental Digital Content, http://links.lww.com/PSYMED/A441). The point estimates for T2DM for those in the highest GRS quartile became a bit larger at the expense of precision.

Discussion

In this study of over 13,000 Dutch adults from the general population, we found in both cross-sectional and longitudinal analyses that participants with a high GRS and a low SEP had the

highest risk for T2DM compared to participants with a low GRS and a high SEP. In addition, a high GRS and a low SEP exacerbated each other's impact in cross-sectional but not in longitudinal analyses. Clinical and behavioral risk factors mostly explained the associations and interactions of a high GRS and a low SEP on T2DM.

A major strength of this study is that T2DM diagnosis, depending on the measurement point, was based on biological markers (FPG and HbA1c), on recorded medication use, and on self-reports in a population-based study sample. In addition, the clinical risk factors general obesity, abdominal obesity, and hypertension were measured by trained research staff. Finally, the GRS was based on the most recent GWAS findings in individuals from European ancestry including only SNPs that were genome-wide significantly associated with T2DM. However, this study also has some limitations that warrant attention. The 5-year follow-up period (median: 57.0 months; 25^{th} – 75^{th} percentile: 47.0 – 68.0 months) is relatively short for demonstrating interaction, maybe leading to an underestimation of the full effects. This was supported by a post-hoc power calculation showing a power of 26.6% to detect interaction in the longitudinal analyses. Larger studies or studies pooling several data-sets, with a longer follow-up period, are needed to compensate for the low incidence. We further had some missing data in the model adjusted for all clinical and behavioral risk factors, implying that their explanatory effect may be slightly larger in particular regarding alcohol consumption.

We demonstrated that a high GRS and a low SEP were separately associated with T2DM, which confirms findings from previous studies (6,44-46) We further showed that these risk factors exacerbated each other's impact on T2DM prevalence but not incidence. A similar result

was recently found for family history of T2DM as indicator for genetic predisposition, although only for women (21) In the longitudinal analyses, we did not find an interaction between a high GRS and low SEP, on top of their separate effect. This contrasts with previous findings that the effect of genetic risk on HbA1c levels is smaller among people with a higher educational level (15) An explanation may be our shorter follow-up period (i.e. 5 vs. 18 years) and our younger study sample (i.e. mean: 48.1 years (SD: 11.4) versus 64% aged >65 (mean not presented)).

There were two noteworthy differences between the findings from the cross-sectional and longitudinal analyses. First, a high GRS was more strongly associated with T2DM in the cross-sectional than in the longitudinal analyses. The effect of a high GRS may have already come to expression cross-sectionally while more time might be needed to lead to effects in the longer term. Second, while low SEP was not cross-sectionally associated with T2DM in participants with a low GRS, a strong association between low SEP and T2DM in participants with a low GRS was found in longitudinal analyses. This contradictory finding deserves attention in future studies because the cross-sectional results suggest that a weak genetic predisposition may buffer the negative effect of low SEP.

We found that the interaction between a high GRS and a low SEP was partly explained by clinical and behavioral risk factors. In general, most T2DM cases can be attributed to dietary habits, physical inactivity, smoking, alcohol consumption and overweight or obesity (47,48) and previous studies have shown that these and other risk factors mediate the relationship between low SEP and T2DM (7-10) This may be due to underlying factors that are associated with low SEP, such as low health literacy (49) Low health literacy has been shown to hamper the

interpretation and translation of information about risk factors into healthy behavior (49) Low health literacy may then contribute largely to the development of diseases with a major behavioral component, like T2DM.

Our findings regarding educational level and household income as indicators for SEP were largely similar. Results might differ somewhat in magnitude when other indicators of SEP are used (e.g. occupational status). However it is likely that the main conclusions would be similar, since all indicators for SEP measure underlying social stratification (29). For T2DM specifically, this is illustrated by a systematic review and meta-analysis on the relation between SEP and T2DM incidence (6). This review showed that the relative risk for T2DM was similar for low educational level, low occupational status, and low income. In practical terms, in care settings it is easier and will evoke less resistance to assess people's educational level than income, because income is often considered private information.

Findings from this study may have some important implications for clinical practice and research. Prevention and intervention strategies aimed at reducing T2DM incidence should target people with a strong genetic predisposition for the disease, especially in the context of a low SEP. This may regard genotyping or family history as its proxy as long as genotyping is not generally available (21,50) These strategies should address individual and contextual factors (51) Individual factors should definitely include health behaviors like physical inactivity and obesity (7,8) and potentially contributing factors such as low health literacy (49) Contextual factors should include, for example, the built environment, which has shown to be important for the development of obesity (52) the most important risk factor for T2DM.

Our cross-sectional findings further suggest that low SEP does not have a detrimental effect regarding T2DM in case of a low GRS. This might imply that prevention measures do not need to target individuals with a low SEP and weak genetic predisposition, but evidently this requires additional study. Future studies should also examine factors contributing to the interaction between strong genetic predisposition and low SEP, such as dietary habits and the physiologic response to chronic stress related to low SEP as they may play an important role in T2DM etiology (11,53). Future research may also need to investigate the role of sleep behavior since several genes have been found to affect both sleep behavior and the risk for T2DM (54). Finally, because our findings are based on people of European ancestry, future studies need to examine whether results are generalizable to other ethnic groups with a different genetic predisposition to T2DM (11)

We conclude that the co-occurrence of a high GRS and low SEP is associated with T2DM prevalence and 5-year incidence. We further conclude that a high GRS and a low SEP exacerbate each other's impact regarding T2DM prevalence but we could not replicate this finding for T2DM incidence. Finally, we conclude that clinical and behavioral risk factors mostly explained the associations and interactions of a high GRS and a low SEP on T2DM. The exacerbation by low SEP of T2DM risk in genetically predisposed people therefore deserves attention in prevention and community care.

Acknowledgements

The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participants. Lifelines is a facility that is open for all researchers. Information on application and data access procedure is summarized on www.lifelines.nl.

Funding

The Lifelines Cohort Study, and generation and management of GWAS genotype data for the Lifelines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation.

References

(1) NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet 2016;387:1513-1530.

(2) Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-2223.

(3) Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. Diabetes Care 2015;38:1777-1803.

(4) Patzer RE, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. Nat Rev Nephrol 2012;8:533-541.

(5) Norhammar A, Bodegard J, Nystrom T, Thuresson M, Eriksson JW, Nathanson D. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. Diabetologia 2016;59:1692-1701.

(6) Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. Int J Epidemiol 2011;40:804-818.

(7) Williams ED, Tapp RJ, Magliano DJ, Shaw JE, Zimmet PZ, Oldenburg BF. Health behaviours, socioeconomic status and diabetes incidence: the Australian Diabetes Obesity and Lifestyle Study (AusDiab). Diabetologia 2010;53:2538-2545.

(8) Agardh EE, Ahlbom A, Andersson T, Efendic S, Grill V, Hallqvist J, Ostenson CG. Explanations of socioeconomic differences in excess risk of type 2 diabetes in Swedish men and women. Diabetes Care 2004;27:716-721.

(9) Maty SC, Everson-Rose SA, Haan MN, Raghunathan TE, Kaplan GA. Education, income, occupation, and the 34-year incidence (1965-99) of Type 2 diabetes in the Alameda County Study. Int J Epidemiol 2005;34:1274-1281.

(10) Stringhini S, Tabak AG, Akbaraly TN, Sabia S, Shipley MJ, Marmot MG, Brunner EJ, Batty GD, Bovet P, Kivimäki M. Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study. BMJ 2012;345:e5452.

(11) Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. Nat Rev Endocrinol 2011;8:228-236.

(12) Kivimaki M, Lawlor DA, Davey Smith G, Kouvonen A, Virtanen M, Elovainio M, Vahtera J. Socioeconomic position, co-occurrence of behavior-related risk factors, and coronary heart disease: the Finnish Public Sector study. Am J Public Health 2007;97:874-879.

(13) Schuit AJ, van Loon AJ, Tijhuis M, Ocke M. Clustering of lifestyle risk factors in a general adult population. Prev Med 2002;35:219-224.

(14) Drong AW, Lindgren CM, McCarthy MI. The genetic and epigenetic basis of type 2 diabetes and obesity. Clin Pharmacol Ther 2012;92:707-715.

(15) Liu SY, Walter S, Marden J, Rehkopf DH, Kubzansky LD, Nguyen T, Glymour MM. Genetic vulnerability to diabetes and obesity: does education offset the risk? Soc Sci Med 2015;127:150-158.

(16) Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk of complex disease. Curr Opin Genet Dev 2008;18:257-263.

(17) Langenberg C, Sharp SJ, Franks PW, Scott RA, Deloukas P, Forouhi NG, et al. Gene-lifestyle interaction and type 2 diabetes: the EPIC interact case-cohort study. PLoS Med 2014;11:e1001647.

(18) Qi L, Cornelis MC, Zhang C, van Dam RM, Hu FB. Genetic predisposition, Western dietary pattern, and the risk of type 2 diabetes in men. Am J Clin Nutr 2009;89:1453-1458.

(19) Qi L, Liang J. Interactions between genetic factors that predict diabetes and dietary factors that ultimately impact on risk of diabetes. Curr Opin Lipidol 2010;21:31-37.

(20) Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. Biol Sex Differ 2015;6:14.

(21) van Zon SK, Snieder H, Bultmann U, Reijneveld SA. The interaction of socioeconomic position and type 2 diabetes mellitus family history: a cross-sectional analysis of the Lifelines Cohort and Biobank Study. BMJ Open 2017;7:e015275.

(22) Scholtens S, Smidt N, Swertz MA, Bakker SJ, Dotinga A, Vonk JM, van Dijk F, van Zon SK, Wijmenga C, Wolffenbuttel BH, Stolk RP. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int J Epidemiol 2015;44:1172-1180.

(23) Nolte IM, van der Most PJ, Alizadeh BZ, de Bakker PI, Boezen HM, Bruinenberg M, Franke L, van der Harst P, Navis G, Postma DS, Rots MG, Stolk RP, Swertz MA, Wolffenbuttel BH, Wijmenga C, Snieder H. Missing heritability: is the gap closing? An analysis of 32 complex traits in the Lifelines Cohort Study. Eur J Hum Genet 2017;25:877-885.

(24) American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014;37 Suppl 1:S81-90.

(25) WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2016. Available from: http://www.whocc.no/atc_ddd_index/. Accessed 14 November 2016.

(26) Amini M, Bashirova D, Prins BP, Corpeleijn E, LifeLines Cohort Study, Bruinenberg M, Franke L, Harst PV, Navis G, Wolffenbuttel BH, Stolk RP, Wijmenga C, Postma DS, Koppelman GH, Boezen HM, Vonk J, Snieder H, Alizadeh BZ. Eosinophil Count Is a Common Factor for Complex Metabolic and Pulmonary Traits and Diseases: The LifeLines Cohort Study. PLoS One 2016;11:e0168480.

(27) Jansen H, Stolk RP, Nolte IM, Kema IP, Wolffenbuttel BH, Snieder H. Determinants of HbA1c in nondiabetic Dutch adults: genetic loci and clinical and lifestyle parameters, and their interactions in the Lifelines Cohort Study. J Intern Med 2013;273:283-293.

(28) V art P, Gansevoort RT, Coresh J, Reijneveld SA, Bultmann U. Socioeconomic measures and CKD in the United States and The Netherlands. Clin J Am Soc Nephrol 2013;8:1685-1693.

(29) Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. Br Med Bull 2007;81-82:21-37.

(30) OECD, European Union, UNESCO Institute for Statistics. I*SCED 2011 Operational Manual: Guidelines for Classifying National Education Programmes and Related Qualifications*. OECD Publishing, 2015.

(31) Veldman K, Bultmann U, Stewart RE, Ormel J, Verhulst FC, Reijneveld SA. Mental health problems and educational attainment in adolescence: 9-year follow-up of the TRAILS study. PLoS One 2014;9:e101751.

(32) Morris AP, Voight BF, Teslovich TM, Ferreira T, Segre AV, Steinthorsdottir V, et al. Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes. Nat Genet 2012;44:981-990.

(33) DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium, South Asian Type 2

Diabetes (SAT2D) Consortium, Mexican American Type 2 Diabetes (MAT2D) Consortium, Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples (T2D-GENES) Consortium, Mahajan A, et al. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet 2014;46:234-244.

(34) Cook JP, Morris AP. Multi-ethnic genome-wide association study identifies novel locus for type 2 diabetes susceptibility. Eur J Hum Genet 2016;24:1175-1180.

(35) Scott RA, Scott LJ, Magi R, Marullo L, Gaulton KJ, Kaakinen M, et al. An Expanded Genome-Wide Association Study of Type 2 Diabetes in Europeans. Diabetes 2017;doi: 10.2337/db16-1253. [Epub ahead of print].

(36) Slagter SN, van Vliet-Ostaptchouk JV, Vonk JM, Boezen HM, Dullaart RP, Kobold AC, et al. Combined effects of smoking and alcohol on metabolic syndrome: the LifeLines cohort study. PLoS One 2014;9:e96406.

(37) World Health Organization. Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation. Geneva, 2008.

(38) Messerli FH, Williams B, Ritz E. Essential hypertension. Lancet 2007;370:591-603.

(39) Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol 2012;41:514-520.

(40) Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet 2006;38:904-909.

(41) Ahlbom A, Alfredsson L. Interaction: A word with two meanings creates confusion. Eur J Epidemiol 2005;20:563-564.

(42) Kendler KS, Gardner CO. Interpretation of interactions: guide for the perplexed. Br J Psychiatry 2010;197:170-171.

(43) Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575-579.

(44) Lall K, Magi R, Morris A, Metspalu A, Fischer K. Personalized risk prediction for type 2 diabetes: the potential of genetic risk scores. Genet Med 2016;19:322-329.

(45) Cornelis MC, Qi L, Zhang C, Kraft P, Manson J, Cai T, Hunter DJ, Hu FB. Joint effects of common genetic variants on the risk for type 2 diabetes in U.S. men and women of European ancestry. Ann Intern Med 2009;150:541-550.

(46) Reiling E, van 't Riet E, Groenewoud MJ, Welschen LM, van Hove EC, Nijpels G, Maassen JA, Dekker JM, 't Hart LM. Combined effects of single-nucleotide polymorphisms in GCK, GCKR, G6PC2 and MTNR1B on fasting plasma glucose and type 2 diabetes risk. Diabetologia 2009;52:1866-1870.

(47) Mozaffarian D, Kamineni A, Carnethon M, Djousse L, Mukamal KJ, Siscovick D. Lifestyle risk factors and new-onset diabetes mellitus in older adults: the cardiovascular health study. Arch Intern Med 2009;169:798-807.

(48) Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willitt WC. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790-797.

(49) van der Heide I, Rademakers J, Schipper M, Droomers M, Sorensen K, Uiters E. Health literacy of Dutch adults: a cross sectional survey. BMC Public Health 2013;13:179.

(50) Heideman WH, Middelkoop BJ, Nierkens V, Stronks K, Verhoeff AP, van Esch SC, Snoek FJ. Changing the odds. What do we learn from prevention studies targeted at people with a positive family history of type 2 diabetes? Prim Care Diabetes 2011;5:215-221.

(51) Solar O, Irwin A. *A conceptual framework for action on the social determinants of health. Social Determinants of Health Discussion Paper 2 (Policy and Practice)*. Geneva, 2010.

(52) Papas MA, Alberg AJ, Ewing R, Helzlsouer KJ, Gary TL, Klassen AC. The built environment and obesity. Epidemiol Rev 2007;29:129-143.

(53) Kelly SJ, Ismail M. Stress and type 2 diabetes: a review of how stress contributes to the development of type 2 diabetes. Annu Rev Public Health 2015;36:441-462.

(54) Karthikeyan R, Marimuthu G, Spence DW, Pandi-Perumal SR, BaHammam AS, Brown GM, Cardinali DP. Should we listen to our clock to prevent type 2 diabetes mellitus? Diabetes Res Clin Pract 2014;106:182-190.

Figure captions

Figure 1 Baseline prevalence and 5-year incidence of type 2 diabetes mellitus across socioeconomic groups per category of genetic risk score

Figure 1

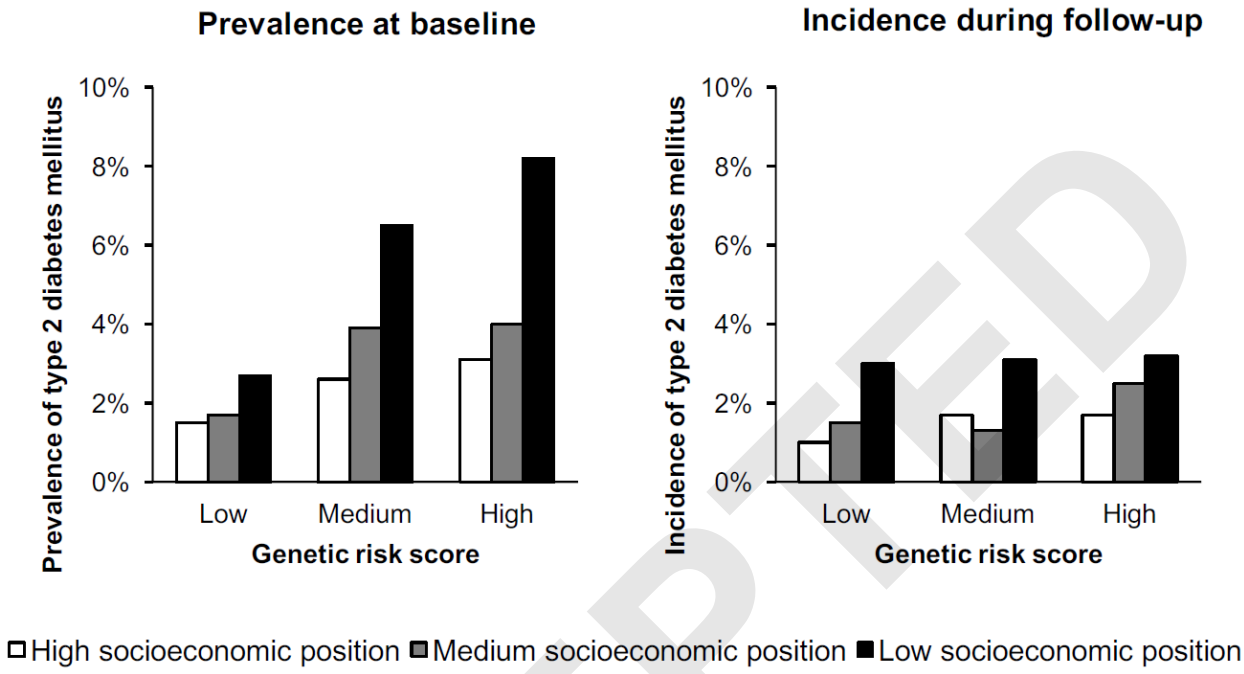

Table 1 Baseline characteristics of the cross-sectional study sample

	Low GRS			**Medium GRS**			**High GRS**		
	High SEP (n=1,118)	**Medium SEP (n=1,630)**	**Low SEP (n=1,596)**	**High SEP (n=1,142)**	**Medium SEP (n=1,582)**	**Low SEP (n=1,619)**	**High SEP (n=1,169)**	**Medium SEP (n=1,565)**	**Low SEP (n=1,606)**
Age, y (mean, SD)	45.5 (10.5)	45.3 (10.1)	52.3 (11.4)	46.4 (11.2)	45.3 (10.0)	51.9 (11.8)	46.1 (10.7)	44.9 (10.3)	52.1 (11.7)
Gender (% F)	53.4	59.6	61.7	52.4	59.6	58.1	51.3	60.7	60.3
Smoking (%)									
Non-smoker	51.3	47.5	37.6	52.3	46.7	40.0	51.7	48.5	39.4
Former smoker	30.1	28.7	34.4	31.6	29.9	31.4	31.0	27.7	31.4
Current smoker	18.6	23.9	28.0	16.0	23.4	28.7	17.2	23.8	29.2
Alcohol consumption (%)									
0 days per week	26.4	35.5	34.1	26.6	33.9	37.7	25.5	34.0	36.4
0-1 days per week	16.3	17.6	17.5	17.2	18.1	15.7	19.2	18.7	16.4
1-3 days per week	35.0	30.9	27.6	32.2	30.5	27.0	31.7	29.7	29.6
>3 days per week	22.2	16.0	20.8	24.0	17.4	19.5	23.6	17.6	17.7
Physical activity (%)									
Active	55.8	53.2	53.5	53.0	50.2	53.8	53.3	54.5	55.4
Moderately active	24.1	24.1	21.6	25.0	25.1	21.2	26.5	22.6	20.6

Inactive	20.1	22.7	24.9	22.0	24.7	25.0	20.2	22.9	24.0
Body mass index (mean, SD)	25.3 (3.8)	26.2 (4.5)	27.1 (4.4)	25.4 (3.6)	26.3 (4.4)	27.1 (4.5)	25.6 (3.7)	26.4 (4.2)	26.9 (4.2)
General obesity (%)									
Underweight	0.4	0.7	0.8	0.4	0.4	0.3	0.9	0.3	0.7
Normal weight	50.1	43.5	33.3	49.3	41.7	32.6	45.9	40.4	33.4
Overweight	39.4	40.2	45.0	41.0	41.9	44.6	40.9	43.2	45.7
Obese	10.1	15.7	21.0	9.3	16.0	22.6	12.2	16.1	20.1
WC, cm F (mean, SD)	85.2 (11.3)	87.7 (12.9)	90.7 (12.0)	84.7 (10.6)	88.1 (12.3)	91.4 (12.7)	85.6 (11.0)	88.2 (11.6)	90.5 (12.1)
WC, cm M (mean, SD)	93.7 (9.4)	95.9 (10.4)	98.9 (11.2)	94.7 (9.1)	95.9 (10.4)	98.6 (10.7)	95.7 (10.1)	96.6 (10.6)	98.3 (10.4)
Abdominal obesity (%)	28.3	36.9	49.9	28.2	38.7	49.8	32.8	39.2	47.6
SBP, mm Hg (mean, SD)	125.8 (14.7)	127.2 (15.3)	131.0 (16.1)	126.3 (15.1)	127.0 (15.2)	131.0 (15.9)	126.8 (15.1)	126.8 (14.9)	132.0 (17.4)
DBP, mm Hg (mean, SD)	74.8 (9.1)	74.8 (9.1)	76.2 (9.2)	74.7 (8.7)	75.0 (8.9)	76.2 (9.0)	75.0 (9.2)	74.7 (8.7)	76.2 (9.4)
Hypertension (%)	22.2	25.2	39.0	23.1	26.5	40.8	26.0	25.9	40.3

Abbreviations: GRS: genetic risk score; SEP: socioeconomic position; SD: standard deviation; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure

Table 2 Associations and interactions of GRS and SEP with T2DM

	n T2DM / n total	OR (95% CI)	RERI (95% CI)
Cross-sectional			
Low GRS			
High SEP	17/1,118	1.00 (ref)	
Medium SEP	28/1,630	1.24 (0.67, 2.29)	
Low SEP	43/1,596	1.13 (0.64, 2.02)	
Medium GRS			
High SEP	30/1,142	1.58 (0.86, 2.90)	
Medium SEP	61/1,582	2.91 (1.68, 5.04)	1.15 (0.06, 2.24)[a]
Low SEP	105/1,619	2.89 (1.71, 4.91)	1.29 (0.32, 2.26)[b]
High GRS			
High SEP	36/1,169	1.96 (1.08, 3.53)	
Medium SEP	62/1,565	3.03 (1.75, 5.25)	0.91 (-0.28, 2.11)[a]
Low SEP	132/1,606	3.84 (2.28, 6.46)	1.85 (0.65, 3.05)[b]
Longitudinal	**n T2DM / n total**	**HR (95% CI)**	**RERI (95% CI)**
Low GRS			
High SEP	11/1,055	1.00 (ref)	
Medium SEP	23/1,511	1.57 (0.77, 3.23)	
Low SEP	43/1,444	2.37 (1.21, 4.61)	
Medium GRS			
High SEP	18/1,063	1.56 (0.73, 3.30)	
Medium SEP	19/1,427	1.40 (0.69, 2.96)	-0.70 (-2.24, 0.84)[a]

Low SEP	43/1,396	2.56 (1.31, 4.99)	-0.41 (-1.95, 1.13)[b]
High GRS			
High SEP	18/1,075	1.46 (0.69, 3.09)	
Medium SEP	35/1,428	2.66 (1.35, 5.24)	0.70 (-0.66, 2.05)[a]
Low SEP	44/1,357	2.71 (1.39, 5.27)	-0.12 (-1.55, 1.32)[b]

Abbreviations: GRS: genetic risk score; SEP: socioeconomic position; T2DM: type 2 diabetes mellitus: OR: odds ratio; CI: confidence interval; RERI: relative excess risk due to interaction; HR: Hazard ratio

ORs/HRs are adjusted for age, age-squared, gender, and principal component scores

[a] RERI T2DM for medium SEP; [b] RERI T2DM for low SEP

Table 3 Associations per category of SEP and GRS with T2DM

	Cross-sectional	Longitudinal
	OR (95% CI)	**HR (95% CI)**
The association of SEP and T2DM per category of GRS		
Low GRS		
High SEP	1.00 (ref)	1.00 (ref)
Medium SEP	1.26 (0.68, 2.33)	1.56 (0.75, 3.21)
Low SEP	1.32 (0.73, 2.38)	2.40 (1.22, 4.75)
Medium GRS		
High SEP	1.00 (ref)	1.00 (ref)
Medium SEP	1.81 (1.15, 2.86)	0.90 (0.47, 1.73)
Low SEP	1.79 (1.16, 2.76)	1.60 (0.90, 2.83)
High GRS		
High SEP	1.00 (ref)	1.00 (ref)
Medium SEP	1.59 (1.03, 2.44)	1.87 (1.05, 3.33)
Low SEP	1.89 (1.27, 2.82)	1.94 (1.10, 3.43)
The association of GRS and T2DM per category of SEP		
High SEP		
Low GRS	1.00 (ref)	1.00 (ref)
Medium GRS	1.53 (0.82, 2.84)	1.59 (0.75, 3.39)
High GRS	2.02 (1.11, 3.68)	1.51 (0.71, 3.21)

Medium SEP		
Low GRS	1.00 (ref)	1.00 (ref)
Medium GRS	2.33 (1.47, 3.69)	0.89 (0.48, 1.64)
High GRS	2.44 (1.54, 3.87)	1.67 (0.98, 2.82)
Low SEP		
Low GRS	1.00 (ref)	1.00 (ref)
Medium GRS	2.56 (1.77, 3.69)	1.05 (0.69, 1.61)
High GRS	3.39 (2.37, 4.84)	1.12 (0.74, 1.71)

Abbreviations: SEP; socioeconomic position; GRS: genetic risk score; T2DM: type 2 diabetes mellitus; OR: odds ratio; CI: confidence interval; HR: hazard ratio

ORs/HRs are adjusted for age, age-squared, gender, and principal component scores

Note: some categories in this Table are similar to those in Table 2 but ORs/HRs may slightly differ because these are result from within category analyses (i.e. different size of the sample being analyzed and therefore a slightly different correction for covariates)

Table 4 Adjusted associations and interactions of GRS and SEP with T2DM #

	Cross-sectional		Longitudinal	
	OR (95% CI)	**RERI (95% CI)**	**HR (95% CI)**	**RERI (95% CI)**
Model 1				
Low GRS				
High SEP	1.00 (ref)		1.00 (ref)	
Medium SEP	1.15 (0.60, 2.21)		1.80 (0.83, 3.92)	
Low SEP	0.84 (0.45, 1.59)		2.57 (1.24, 5.35)	
Medium GRS				
High SEP	1.45 (0.76, 2.79)		1.66 (0.73, 3.77)	
Medium SEP	2.35 (1.30, 4.27)	0.83 (-0.16, 1.81)[a]	1.38 (0.61, 3.12)	-1.08 (-2.99, 0.83)[a]
Low SEP	2.32 (1.31, 4.11)	1.09 (0.20, 1.98)[b]	2.79 (1.34, 5.80)	-0.60 (-2.39, 1.20)[b]
High GRS				
High SEP	2.19 (1.18, 4.07)		1.65 (0.73, 3.74)	
Medium SEP	2.32 (1.27, 4.23)	0.01 (-1.30, 1.31)[a]	2.92 (1.39, 6.13)	0.46 (-1.11, 2.03)[a]
Low SEP	3.10 (1.76, 5.43)	1.20 (0.07, 2.32)[b]	2.68 (1.29, 5.60)	-0.60 (-2.38, 1.18)[b]
Model 2				
Low GRS				
High SEP	1.00 (ref)		1.00 (ref)	
Medium SEP	1.02 (0.53, 1.97)		1.56 (0.72, 3.39)	
Low SEP	0.69 (0.36, 1.31)		1.99 (0.95, 4.14)	
Medium GRS				
High SEP	1.57 (0.81, 3.03)		1.66 (0.73, 3.76)	
Medium SEP	2.10 (1.15, 3.84)	0.59 (-0.40, 1.57)[a]	1.21 (0.53, 2.74)	-0.98 (-2.76, 0.81)[a]
Low SEP	1.89 (1.06, 3.38)	0.74 (-0.11, 1.60)[b]	2.20 (1.06, 4.58)	-0.59 (-2.22, 1.05)[b]

High GRS				
High SEP	2.09 (1.12, 3.91)		1.42 (0.63, 3.23)	
Medium SEP	2.02 (1.10, 3.71)	-0.11 (-1.36, 1.13)[a]	2.46 (1.17, 5.16)	0.59 (-0.69, 1.88)[a]
Low SEP	2.65 (1.50, 4.69)	0.95 (-0.07, 1.96)[b]	2.22 (1.06, 4.63)	-0.30 (-1.79, 1.19)[b]
Model 3				
Low GRS				
High SEP	1.00 (ref)		1.00 (ref)	
Medium SEP	1.00 (0.51, 1.93)		1.48 (0.68, 3.23)	
Low SEP	0.67 (0.35, 1.27)		1.83 (0.88, 3.81)	
Medium GRS				
High SEP	1.56 (0.81, 3.02)		1.64 (0.72, 3.72)	
Medium SEP	2.02 (1.10, 3.69)	0.50 (-0.48, 1.49)[a]	1.16 (0.51, 2.64)	-0.99 (-2.77, 0.79)[a]
Low SEP	1.76 (0.98, 3.14)	0.65 (-0.20, 1.50)[b]	2.02 (0.97, 4.20)	-0.49 (-1.99, 1.01)[b]
High GRS				
High SEP	2.06 (1.10, 3.86)		1.37 (0.60, 3.11)	
Medium SEP	1.97 (1.07, 3.63)	-0.09 (-1.33, 1.15)[a]	2.37 (1.13, 4.97)	0.62 (-0.63, 1.86)[a]
Low SEP	2.51 (1.42, 4.44)	0.86 (-0.14, 1.85)[b]	2.06 (0.99, 4.31)	-0.20 (-1.60, 1.20)[b]

#Adjustment regards:

Model 1: age, age-squared, gender, PCs, smoking, alcohol consumption, physical activity

Model 2: model 1 plus general weight status, abdominal obesity

Model 3: model 2 plus hypertension

Abbreviations: GRS: genetic risk score; SEP: socioeconomic position; T2DM: type 2 diabetes mellitus; OR: odds ratio; CI: confidence interval; RERI: relative excess risk due to interaction; HR: hazard ratio

[a] RERI T2DM for medium SEP; [b] RERI T2DM for low SEP