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ARTICLE

Associations of polysocial risk score, lifestyle and genetic factors with incident type 2 diabetes: a prospective cohort study

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Abstract

Aim/hypothesis We aimed to investigate the association between polysocial risk score (PsRS), an estimator of individual-level exposure to cumulative social risks, and incident type 2 diabetes in the UK Biobank study.

Methods This study includes 319,832 participants who were free of diabetes, cardiovascular disease and cancer at baseline in the UK Biobank study. The PsRS was calculated by counting the 12 social determinants of health from three social risk domains (namely socioeconomic status, psychosocial factors, and neighbourhood and living environment) that had a statistically significant association with incident type 2 diabetes after Bonferroni correction. A healthy lifestyle score was calculated using information on smoking status, alcohol intake, physical activity, diet quality and sleep quality. A genetic risk score was calculated using 403 SNPs that showed significant genome-wide associations with type 2 diabetes in people of European descent. The Cox proportional hazards model was used to analyse the association between the PsRS and incident type 2 diabetes.

Results During a median follow-up period of 8.7 years, 4427 participants were diagnosed with type 2 diabetes. After adjustment for major confounders, an intermediate PsRS (4–6) and high PsRS (≥7) was associated with higher risks of developing type 2 diabetes with the HRs being 1.38 (95% CI 1.26, 1.52) and 2.02 (95% CI 1.83, 2.22), respectively, compared with those with a low PsRS (≤3). In addition, an intermediate to high PsRS accounted for approximately 34% (95% CI 29, 39) of new-onset type 2 diabetes cases. A healthy lifestyle slightly, but significantly, mitigated PsRS-related risks of type 2 diabetes ($p_{interaction}$=0.030). In addition, the additive interactions between PsRS and genetic predisposition led to 15% (95% CI 13, 17; p<0.001) of new-onset type 2 diabetes cases ($p_{interaction}$<0.001).

Conclusions/interpretation A higher PsRS was related to increased risks of type 2 diabetes. Adherence to a healthy lifestyle may attenuate elevated diabetes risks due to social vulnerability. Genetic susceptibility and disadvantaged social status may act synergistically, resulting in additional risks for type 2 diabetes.

Keywords Genetic predisposition · Lifestyle · Polysocial risk score · Type 2 diabetes · UK Biobank

Abbreviations

GRS Genetic risk score
MET Metabolic-equivalent
PsRS Polysocial risk score
SBP Systolic blood pressure

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Research in context

What is already known about this subject?

- Disadvantaged social status is linked to an increased incidence of type 2 diabetes
- The associations of a single social risk factor with incident type 2 diabetes have been described previously, but the combined effects of social risk factors from various domains remain less studied

What is the key question?

- How is a newly developed polysocial risk score (PsRS), an estimator of cumulative exposure to adverse social factors, associated with the incidence of type 2 diabetes?

What are the new findings?

- In this population-based prospective cohort study among 319,832 people in the UK, a high PsRS was associated with an elevated risk of developing type 2 diabetes
- Adherence to a favourable healthy lifestyle may significantly mitigate the PsRS-related risk of developing type 2 diabetes
- Disadvantaged social status and genetic susceptibility may act synergistically, leading to an excess risk of incident type 2 diabetes in this study

How might this impact on clinical practice in the foreseeable future?

- The newly developed PsRS may be used as a simple but informative tool to identify socially disadvantaged people and to address the escalating prevalence of type 2 diabetes

Introduction

The global epidemic of type 2 diabetes has continued to grow in recent years [1, 2]. The International Diabetes Federation has estimated that the number of people with diabetes worldwide will increase from 537 million in 2021 to 783 million in 2045 [3]. The onset of type 2 diabetes is contributed to by a matrix of genetic susceptibility, lifestyle, socioeconomic status, psychosocial factors and living environment [4, 5]. Genome-wide association studies have established the predominant role of genetic predisposition in developing type 2 diabetes [6, 7]. The results from previous randomised clinical trials also provided strong evidence for use of lifestyle intervention methods in preventing type 2 diabetes [8]. Nevertheless, genetic predisposition and lifestyle factors cannot fully explain the escalating prevalence of type 2 diabetes [4, 5].

Disadvantaged social status has been shown to be an important upstream determinant of health, outweighing medical care [9, 10]. Previous observational studies have underscored the important roles of social determinants of health in developing type 2 diabetes. For example, low education level and economic instability were associated with a higher incidence of type 2 diabetes and diabetes complications and worse adherence with diabetes management programmes [11–13]. Sustained psychosocial stress may lead to chronic allostatic load and glucose dysmetabolism, thus promoting the development of type 2 diabetes [14, 15]. However, most previous epidemiological studies only quantified the contribution of a single social determinant of health, overlooking their complex interconnection. Social determinants of health in different domains affect health in an aggregated way [16]. Ignoring the synergistic effects of social risk factors from various domains undoubtedly undermines efforts to identify socially disadvantaged people and implement social interventions to address social inequities [16].

A previous study has suggested that combinations of unhealthy lifestyle factors are related to disproportionate harm in people with socioeconomic deprivation [17]. Another study argued that lifestyle factors only mediate a fairly small proportion of the socioeconomic inequity in mortality risk and cardiovascular health [18]. However, it remains unclear whether lifestyle factors interact with social determinants of health related to type 2 diabetes incidence. Moreover, it has not been determined whether disadvantaged social status leads to excess risks of developing type 2 diabetes beyond genetic predisposition.

Therefore, we constructed a polysocial risk score (PsRS) to evaluate participant-level overall exposure to social risks, to investigate associations of the PsRS with the risks of developing type 2 diabetes, and to explore potential interactions

between the PsRS and lifestyles/genetic susceptibilities related to incident type 2 diabetes in the UK Biobank study.

Methods

Study population The detailed study design and characteristics of the UK Biobank have been described previously [19]. In brief, the UK Biobank study recruited over half a million people from the general population across England, Wales and Scotland between 2006 and 2010. At their baseline visit to the assessment centre, the participants completed nurse-administrated touchscreen questionnaires about diets, lifestyle factors and health-related information, underwent extensive physical examination, and provided biological samples for genotyping. All participants provided written informed consent. The present study was conducted under Application Number 44430 of the UK Biobank data resource.

In the present study, we excluded those with diagnosed cardiovascular disease (n=34,142), diabetes (n=30,589) or cancer (n=44,035) at baseline, or those with missing data for calculation of the PsRS (n=107,517) leaving a total of 319,832 eligible participants in the primary analysis (see Electronic supplementary material [ESM] Fig. 1). In the PsRS–gene interaction analysis, we excluded participants who were not of white British descent (n=33,557) or with missing genotyping data (n=6666).

Ascertainment of type 2 diabetes

The baseline type 2 diabetes status was determined using a validated algorithm based on self-reported diagnosis, prescription of glucose-lowering medication, and blood glucose and HbA_{1c} levels [20]. Data on hospital inpatient admissions were obtained via linkage with the Hospital Episode Statistics database, the Patient Episode Database for Wales and the Scottish Morbidity Record for participants from England, Wales and Scotland, respectively. The International Classification of Diseases, Tenth Revision (http://apps.who.int/classifications/icd10/browse/2016/en) was used to identify incident type 2 diabetes (Read code E11; https://digital.nhs.uk/article/1104/Read-Codes).

Calculation of PsRS

The Healthy People 2030 Initiative (https://health.gov/healthypeople) has announced a framework that outlines five key domains of social determinants of health, namely economic stability, education access and quality, healthcare access and quality, neighbourhood and built environment, and social and community context. In this study, we further re-classified 17 pre-selected social determinants of health into three domains, namely socioeconomic status, psychosocial factors, and neighbourhood and living environment, according to previous literature [9, 21–23] and data availability for the UK Biobank (see ESM Table 1 for details). For socioeconomic status, the participant was considered at risk if (1) their total household income before tax was less than £31,000 (low household income); (2) their education level was lower than college (low education attainment); (3) their education was below the median education quality score (poor education quality); (4) they were not in any paid employment or self-employed. For psychosocial factors, the participant was considered as at risk if they (1) lived alone; (2) cannot confide in someone nearby at least once a week (lack of social support); (3) attended any group activities less often than once a week (social inactivity); (4) visited friends/family or had them to visit once a week or less often (social isolation); (5) had experienced illness, injury, bereavement or stress within last 2 years (emotional distress); (6) had diagnosed psychiatric disorders including anxiety, depression and bipolar disorder, or had ever self-harmed (diagnosed psychiatric disorder) [24]. For neighbourhood and living environment, the participant was considered as at risk if (1) their score for the Townsend deprivation index was above the median (area-level material deprivation); (2) the crime score for their neighbourhood was above the median (high local crime rate); (3) their housing score was above the median (poor housing quality); (4) they did not own their current accommodation outright (instable accommodation); (5–7) the percentages of home location buffer classed as greenspace (greenspace remoteness), water (bluespace remoteness) and natural land (natural environment remoteness) were below the median. The crime score recorded the incidence of major crime types in a certain area. The housing score measured overcrowding and lack of central heating in the house. The education score indicated the local extent of deprivation relating to education, training and skills. The crime, housing and education scores were provided by a UK government qualitative study of deprived areas in British local councils, which are publicly available. We calculated the PsRS by counting the dichotomised social determinants of health, with a higher PsRS indicating greater social vulnerability. A social determinant of health was included in the calculation of PsRS if it showed a significant association with incident type 2 diabetes with a Bonferroni's corrected p value <0.0029 (0.05/17 comparisons) in the fully adjusted model.

Assessment of lifestyle factors We established a healthy lifestyle score based on five behavioural lifestyle factors, namely smoking status, alcohol intake, physical activity, diet quality and sleep quality, according to guidance from the American Diabetes Association and previous literature [25–27]. Daily alcohol intake (g/day) was assessed using the baseline touchscreen questionnaire in terms of drinking frequency and beverage type. Physical activity was assessed based on

the duration and frequency of walking, moderate and vigorous activities using a short form of the International Physical Activity Questionnaire [28]. Total physical activity was expressed as metabolic-equivalent (MET)-h/week. Diet was assessed via a food frequency questionnaire at baseline. A diet quality score was calculated according to the intake of fruits, vegetables, processed meat, red meat, fish, whole grains and refined grains (see ESM Methods for details) [19, 29]. A sleep quality score was calculated based on chronotype, sleep duration, frequency of insomnia, snoring and daytime sleepiness (see ESM Methods for details) [30]. We assigned one point to each healthy lifestyle factor: never smoking, low to moderate alcohol intake (>0 and ≤28 g/day for men; >0 and ≤14 g/day for women), adequate physical activity (meeting any of the five criteria: ≥150 min/week of moderate activity, or ≥75 min/week of vigorous activity, or ≥150 min/week of combined moderate and vigorous activity, or moderate activity ≥5 times/week, or vigorous activity ≥1 time/week) [31], healthy diet (diet quality score ≥4) and healthy sleep pattern (sleep quality score ≥4). A higher healthy lifestyle score indicated better adherence to an ideal lifestyle. We assigned participants into lifestyle groups according to their healthy lifestyle scores: favourable (scores of 4 or 5), intermediate (scores of 2 or 3) and unfavourable (scores of 0 or 1).

Calculation of genetic risk score The detailed genotyping process and arrays used in the UK Biobank have been described previously [32, 33]. In this study, we established a weighted genetic risk score (GRS) based on 403 SNPs that had significant genome-wide associations with type 2 diabetes in people of European descent [6]. The effect size of each SNP was coded as 0, 1 and 2 according to the number of risk alleles, and the corresponding β coefficient was used as the weighting factor [6]. We classified participants as at low, intermediate or high genetic risk of type 2 diabetes according to the tertiles of GRS.

Other covariates Information on age and sex was collected during the baseline visit to the assessment centre. Body weight and height were measured for calculation of BMI. Systolic blood pressure (SBP) was measured by either an automated sphygmomanometer (Omron, USA) or a manual sphygmomanometer.

Statistical analysis Between-group differences in baseline characteristics were compared using one-way ANOVA or χ^2 test when appropriate. We used a Cox proportional hazards model to analyse the associations between PsRS and incidence of type 2 diabetes, with time-to-event as the time scale. The assumptions of the Cox proportional hazards model were assessed using Schoenfeld residuals. The basal model was adjusted for age (continuous) and sex. The fully adjusted model was additionally adjusted for BMI (continuous), SBP (sex-specific quintiles of mmHg), smoking status (never, previous and current smokers), alcohol intake (sex-specific quintiles of g/day), physical activity (sex-specific quintiles of MET-h/week), diet quality score (continuous) and sleep quality score (continuous). A p value for trend was calculated treating PsRS as a continuous variable. The potential non-linear relationship between PsRS and incident type 2 diabetes was examined by restricted cubic splines with knots placed at the 10th, 50th and 90th percentiles of PsRS. The 5-year cumulative incidence of type 2 diabetes per 1000 person-years was calculated using the Nelson–Aalen method [34]. We also calculated the population-attributable fraction [35], an estimate of the proportions of type 2 diabetes events attributed to individual social determinants of health and PsRS. The additive interactions between PsRS, lifestyle score and GRS were analysed by calculating the attributable proportion for additive interaction, and testing whether the relative excess risk due to interaction equals zero [36, 37].

In the sensitivity analysis, we excluded type 2 diabetes cases that occurred in the first 5 years of follow-up, excluded participants with hyperglycaemia (glucose ≥7.0 mmol/l) at baseline, and additionally adjusted for GRS (continuous), the first ten genetic principal components, and genotyping batch. We also included inadequate physical activity and current/ever smoking as social determinants of health in calculating the PsRS according to the Healthy People 2030 Initiative. To test the robustness of the primary analysis, we also calculated a weighted PsRS using the β coefficients of individual social determinants of health obtained from univariate analysis as the weighting factors. We compared the predictive performance of the unweighted and weighted PsRS using Harrell's C index [38]. Statistical analysis was performed using Stata/MP version 16.0 (StataCorp, USA). Statistical significance was set at $p<0.05$.

Ethical approval The UK Biobank study was approved by the National Information Governance Board for Health and Social Care in England and Wales, the Community Health Index Advisory Group in Scotland, and the Northwest Multicenter Research Ethics Committee. All participants gave written informed consent. This study was also approved by the Ethical Committee of Peking University (Beijing, China).

Results

Calculation of PsRS We included 12 of the 17 pre-selected social determinants of health in the PsRS calculation; these were consistently related to markedly increased incidence of type 2 diabetes after Bonferroni correction, and thus the PsRS value ranged from 0 to 12 (ESM Table 2). The percentages of at-risk participants for each social determinant of health ranged from 18.3% for living alone to 63.5% for low

education attainment, with most being approximately 50% (ESM Table 2). Among the 12 social determinants of health, the fully adjusted HRs ranged from 1.10 (95% CI 1.03, 1.16) for natural environmental remoteness to 1.45 (95% CI 1.35, 1.54) for low household income. We further assigned participants into low (PsRS ≤3), intermediate (PsRS 4–6) and high (PsRS ≥7) social risk groups according to their PsRS.

Baseline characteristics stratified by PsRS categories The baseline characteristics of participants stratified by PsRS categories are shown in Table 1. Of the 319,832 eligible UK Biobank participants, 24.8%, 47.1% and 28.1% were categorised into the low, intermediate and high social risk groups. Compared with participants at either intermediate or high social risk, those in the favourably low social risk group were more likely to be younger, have a healthier BMI (between 18.5 and 25 kg/m^2), never have smoked, have a low to moderate alcohol intake, exercise adequately, and eat and sleep better (all p values<0.001).

PsRS and incident type 2 diabetes During a median follow-up of 8.7 years (IQR 8.1–9.3 years; 2,764,815 total person-years), we identified 4427 incident cases of type 2 diabetes. The 5-year cumulative incidence of type 2 diabetes was 2.74 (95% CI 2.40, 3.13), 4.87 (95% CI 4.53, 5.24) and 9.18 (95% CI 8.57, 8.83) per 1000 person-years for participants with low, intermediate and high social risks, respectively (Fig. 1a). The fully adjusted model showed that participants with intermediate and high social risk had significantly elevated risks of developing type 2 diabetes with the HRs being 1.38 (95% CI 1.26, 1.52) and 2.02 (95% CI 1.83, 2.22), respectively, compared with those with low social risk (Table 2). Each point increment in PsRS was associated with a 13% (95% CI 12, 15) higher incidence of type 2 diabetes (p_{trend}<0.001). The association between PsRS and incident type 2 diabetes tended to be linear rather than non-linear or quadratic ($p_{non\text{-}linearity}$=0.189, Fig. 1b). In addition, an intermediate to high PsRS (4–12) accounted for approximately 34% (95% CI 29, 39) of new-onset type 2 diabetes cases in this study.

The sensitivity analysis revealed that the results of the primary analysis remained stable when excluding type 2 diabetes cases that occurred in the first 5 years of follow-up, excluding participants with a baseline blood glucose ≥7.0 mmol/l, additionally adjusting for GRS, the first ten genetic principal components, and genotyping batch, or including inadequate physical activity and current/ever smoking when calculating the PsRS (ESM Table 3). In addition, the unweighted and weighted PsRS had similar predictive performance for incident type 2 diabetes as indicated by Harrell's C index (ESM Tables 4 and 5).

PsRS, healthy lifestyle and incident type 2 diabetes

Maintaining a favourable lifestyle was associated with a lower risk of developing type 2 diabetes when compared with those who had an unfavourable lifestyle (HR 0.61, 95% CI 0.54,

Table 1 Baseline characteristics of participants

Variable	Polysocial risk score		
	Low (≤3)	Intermediate (4–6)	High (≥7)
Participants (%)	24.8	47.1	28.1
Age (years)	55.0 ± 7.6	55.6 ± 8.1	55.5 ± 8.4
Male (%)	51.8	45.6	41.9
BMI (kg/m^2)	26.4 ± 4.0	27.0 ± 4.4	27.8 ± 5.1
BMI ≥18.5 and <25 kg/m^2 (%)	38.9	34.8	30.1
SBP (mmHg)	137 ± 18	137 ± 18	137 ± 18
Never smoked (%)	63.5	56.9	49.0
Alcohol intake (g/day)	12.8 (5.1–23.8)	10.5 (2.3–22.7)	7.4 (0.2–20.4)
Low to moderate alcohol intake (%)	50.9	49.3	42.8
Physical activity (MET-h/week)	28.8 (15.4–47.5)	28.8 (16.6–52.5)	28.8 (16.9–54.2)
Adequate physical activity (%)	74.6	72.5	67.9
Diet quality score	3.4 ± 1.5	3.3 ± 1.6	3.2 ± 1.6
Sleep quality score	3.2 ± 1.0	3.1 ± 1.0	2.9 ± 1.0

Continuous variables are expressed as means ± SD or median (interquartile range) when appropriate.

Low to moderate alcohol intake was defined as >0 and ≤14 g/day for women >0 and ≤28 g/day for men, respectively

Adequate physical activity was defined as ≥150 min/week of moderate activity, or ≥75 min/week of vigorous activity, or ≥150 min/week of combined moderate and vigorous activity, ≥5 times/week of moderate activity, or ≥1 time/week of vigorous activity

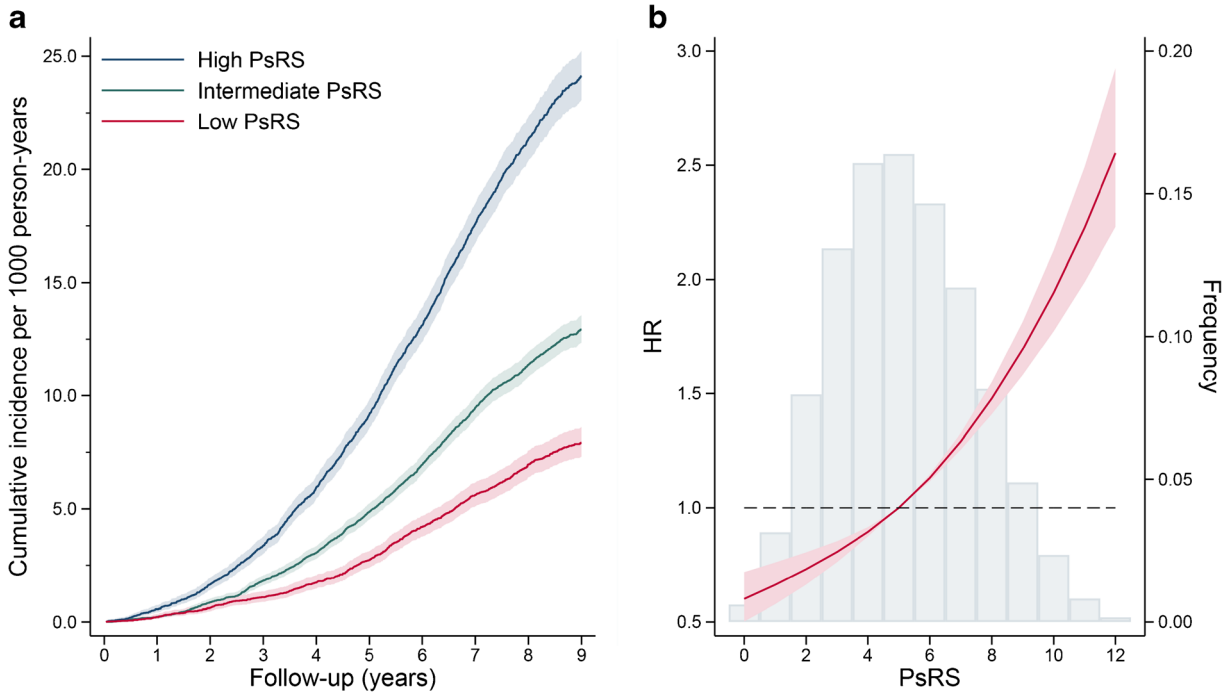

Fig. 1 Association of PsRS with incident type 2 diabetes. (**a**) Cumulative incidence of type 2 diabetes stratified by PsRS category. (**b**) Distribution of PsRS (frequency, on the right axis), and the associations between PsRS and incident type 2 diabetes (HR, on the left axis)

0.69, ESM Table 6). We observed a slight but statistically significant additive interaction between PsRS and healthy lifestyle score for incident type 2 diabetes (p for additive interaction=0.030, Fig. 2). A favourable lifestyle was consistently related to a lower incidence of type 2 diabetes across all PsRS groups. Notably, the PsRS–lifestyle joint analysis revealed that following a favourable lifestyle may substantially mitigate the detrimental effects of social vulnerability on incident type 2 diabetes as indicated by an attributable proportion for additive interaction between PsRS and healthy lifestyle of −37% (95% CI −71, −3, p=0.032). Maintaining a favourable lifestyle or unfavourable lifestyle was related to 29% (95% CI 4, 61) and 103% (95% CI 72, 140) higher risks of type 2 diabetes, respectively, in participants with a high PsRS (≥7).

PsRS, genetic predisposition and incident type 2 diabetes In the present study, participants in the highest tertile of GRS had an elevated risk of type 2 diabetes (HR 2.09, 95% CI 1.92, 2.27, ESM Table 7). In addition, we found a significant additive interaction between genetic predisposition and PsRS in the context of incident type 2 diabetes (p for additive interaction <0.001, Fig. 3). Participants with a higher PsRS were related to an increased incidence of type 2 diabetes across all GRS groups. In addition, the additive interaction between PsRS and GRS explained approximately 15% (95% CI 13, 17, p<0.001) of new-onset type 2 diabetes cases,

Table 2 Association of PsRS with incident type 2 diabetes

	PsRS					
	Low (≤3)	Intermediate (4–6)	High (≥7)	Per point increment	P_{trend}	Population-attributable fraction
Cases	592	1828	2007			
Person-years	694,659	1,304,321	765,835			
Age- and sex-adjusted HR	1.00	1.66 (1.51, 1.82)	3.17 (2.89, 3.48)	1.23 (1.21, 1.24)	<0.001	47 (44, 51)
Fully adjusted HR	1.00	1.38 (1.26, 1.52)	2.02 (1.83, 2.22)	1.13 (1.12, 1.15)	<0.001	34 (29, 39)

The HRs and 95% CIs were calculated using the Cox proportional hazards model. The fully adjusted model adjusted for age, sex, BMI, SBP, smoking status, alcohol intake, physical activity, diet quality score and sleep quality score.

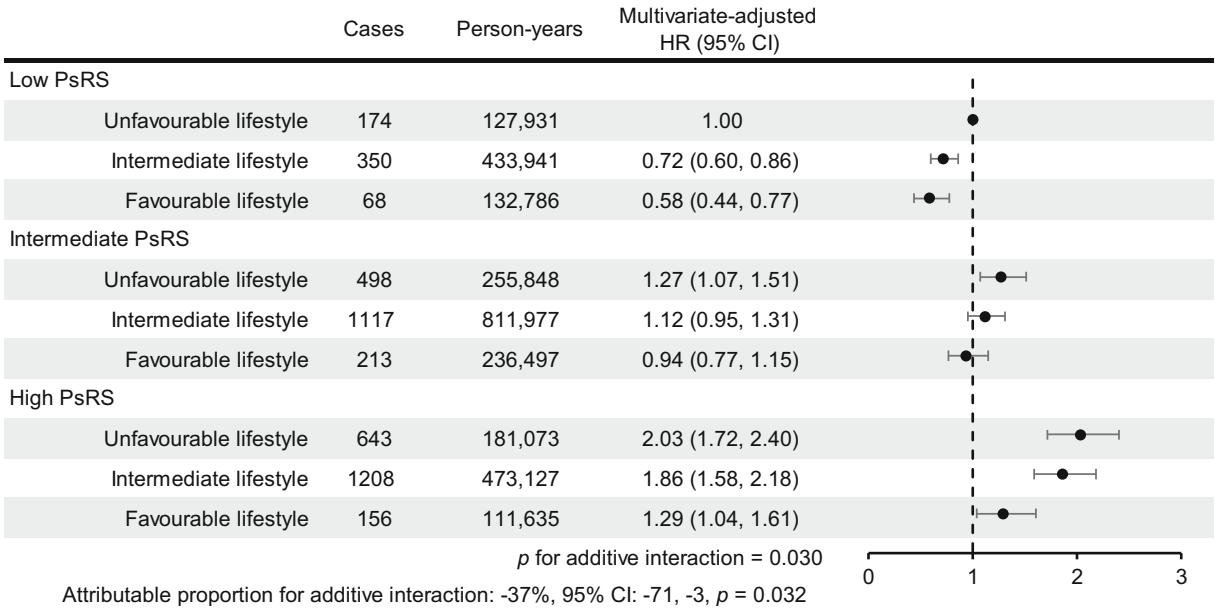

Fig. 2 Joint analysis of the associations of PsRS and lifestyle score with incident type 2 diabetes

suggesting that disadvantaged social status may significantly exacerbate the associations between genetic susceptibility and incident type 2 diabetes.

Discussion

In this population-based cohort study among 319,832 UK Biobank participants, we constructed a PsRS by counting the 12 social determinants of health from various domains to estimate participant-level exposure to cumulative social risks. We found that participants with a high PsRS (≥7) had an almost twofold higher risk of developing type 2 diabetes compared with those with a favourably low PsRS (0–3). Adherence to a healthy lifestyle may slightly but significantly attenuate the observed relationships between PsRS and type 2 diabetes incidence. In addition, genetic predisposition and disadvantaged social status may act synergistically, leading to an excess risk of incident type 2 diabetes.

Our findings are in accordance with previous studies showing increased risk of type 2 diabetes due to social vulnerabilities. For example, individuals with lower household income and education levels showed a higher incidence of type 2 diabetes and diabetes complications [39]. A high proportion

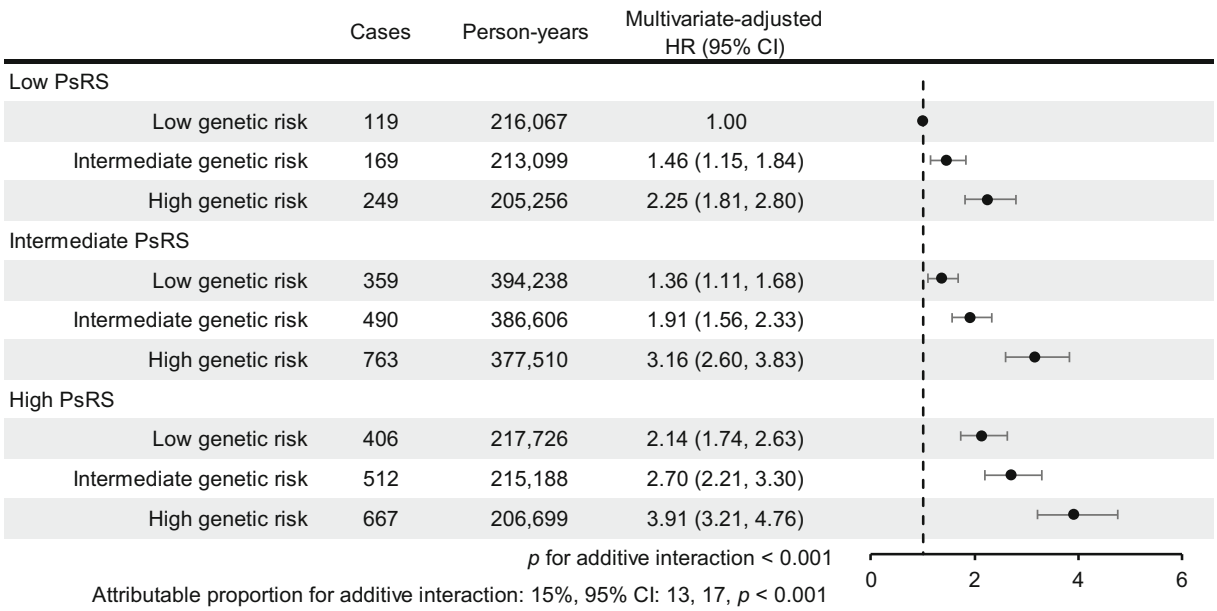

Fig. 3 Joint analysis of the associations of PsRS and GRS with incident type 2 diabetes

of natural environment in the neighbourhood was related to a lower incidence of type 2 diabetes [40, 41]. However, previous studies only examined the contributions of one or a few adverse social factors to the incidence of type 2 diabetes and did not consider the interconnection among them. In the present study, a PsRS that incorporated 12 social determinants of health was associated with disproportionately higher risk of incident type 2 diabetes. An intermediate to high PsRS accounted for approximately 34% of new-onset type 2 diabetes cases among the UK Biobank participants. Given the high and increasing economic and healthcare burden from type 2 diabetes [42], the newly developed PsRS may be a simple but informative tool for the healthcare system to identify a socially disadvantaged population and perform social interventions to address social inequalities.

The mechanisms underlying the observed PsRS–diabetes associations are not fully understood. One possible explanation for the PsRS-associated risk of type 2 diabetes is that greater social vulnerabilities are often linked to a lack of health literacy and inability to access, understand and use health information to make appropriate health-related decisions [43, 44]. Management of type 2 diabetes is difficult, and requires sufficient levels of health literacy and frequent contact with clinicians [45]. Suboptimal diabetes self-management has been reported to be common among socially disadvantaged people [46, 47]. However, there are no direct measurements of health literacy in the UK Biobank yet, and thus whether health literacy mediates the association of social vulnerabilities with incident type 2 diabetes remains largely unknown. Future studies are required to disentangle the roles of health literacy in disadvantaged social status-related type 2 diabetes risks.

In the present study, behavioural lifestyle factors had significant interactions with PsRS, in that a favourable lifestyle substantially mitigated the risks of type 2 diabetes, particularly among people with the highest level of social vulnerabilities. Lifestyle management is a fundamental part of diabetes prevention and treatment [26]. Both observational and intervention studies have demonstrated the protective effects of healthy lifestyle factors against incident type 2 diabetes [33, 48–51]. Adherence to a healthier lifestyle was associated with a reduction in the incidence of type 2 diabetes and a reduction of adverse health outcomes among diabetic patients [52]. We also showed that participants with low social risks (PsRS ≤3) maintained a significantly healthier lifestyle at baseline compared with those with intermediate or high social risks. Collectively, these findings imply that lifestyle modification should be encouraged when tackling social inequalities among socially disadvantaged people.

Genetic susceptibility and gene–environment interaction contribute considerably to the epidemic of type 2 diabetes [4, 53]. In this study, we found a strong additive interaction between genetic predisposition and social vulnerabilities in terms of incident type 2 diabetes, suggesting that PsRS-related excess risks of type 2 diabetes may partly result from the genetic background of participants. In addition, the positive relationship between PsRS and type 2 diabetes risks was consistent across all social risk categories among the UK Biobank participants. Given the observational design of the present study, more research is required to test whether the genetic predisposition to type 2 diabetes may modify the effectiveness of social intervention in the future.

This study had several strengths. The comprehensive data collection of UK Biobank enabled us to establish the PsRS, which comprehensively estimated participant-level total exposure to social risks from various domains. In addition, the extremely large sample size of UK Biobank allowed us to performed a joint analysis between PsRS, lifestyle, and genetic susceptibility with adequate statistical power to test the interactions between PsRS and lifestyle/genetic factors.

However, the present study also had limitations. First, due to the prospective cohort design of UK Biobank, we cannot make any causality inference regarding PsRS and incident type 2 diabetes. The possibilities of reverse causation and residual confounding cannot be entirely ruled out, even though the sensitivity analysis revealed the robustness of our results. Second, the data on social determinants of health and lifestyle factors were self-reported and assessed only once, which may result in measurement errors. Repeated measurements are required to capture long-term changes in PsRS and lifestyle factors. Third, we only included British white participants in the analysis of PsRS–gene interaction. The observed PsRS–gene interaction requires verification in other races/ethnicities as diabetes risks vary dramatically across race/ethnicity groups [54]. Fourth, the UK Biobank participants tended to be more affluent and had better socioeconomic status than people in less developed countries, thus limiting the generalisability of our results [17, 55]. Fifth, the PsRS was established by counting social determinants of health, assuming that each component has the same effects on health, which may not be true. However, we also calculated a weighted PsRS and found similar predictive performance between the unweighted and weighted PsRS regarding incident type 2 diabetes.

In conclusion, our findings indicate that the PsRS, calculated as the score for 12 social determinants of health, was associated with an elevated incidence of type 2 diabetes among UK Biobank participants. Maintaining a healthy lifestyle may neutralise PsRS-related risks of type 2 diabetes. Our results further highlight the necessity of developing social intervention and social support approaches to address health determinants beyond the traditional clinical risk factors for type 2 diabetes.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-022-05761-y.

Data availability Data are available in a public open-access repository. This research was performed using the UK Biobank Resource under Application Number 44430. The UK Biobank data are available on application to the UK Biobank (www.ukbiobank.ac.uk/).

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Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement YZ, YL, ZZ, DL and TH conceived and designed the research. YZ, YL, and TH had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. YZ and YL drafted the paper and performed the data analysis. All authors contributed to the statistical analysis, critically reviewed the manuscript during the writing process, and approved the final version to be published. TH is the guarantor for this study.

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