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ARTICLE

Obesity, unfavourable lifestyle and genetic risk of type 2 diabetes: a case-cohort study

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Abstract

Aims/hypothesis We aimed to investigate whether the impact of obesity and unfavourable lifestyle on type 2 diabetes risk is accentuated by genetic predisposition.

Methods We examined the joint association of genetic predisposition, obesity and unfavourable lifestyle with incident type 2 diabetes using a case-cohort study nested within the Diet, Cancer and Health cohort in Denmark. The study sample included 4729 individuals who developed type 2 diabetes during a median 14.7 years of follow-up, and a randomly selected cohort sample of 5402 individuals. Genetic predisposition was quantified using a genetic risk score (GRS) comprising 193 known type 2 diabetes-associated loci (excluding known BMI loci) and stratified into low (quintile 1), intermediate and high (quintile 5) genetic risk groups. Lifestyle was assessed by a lifestyle score composed of smoking, alcohol consumption, physical activity and diet. We used Prentice-weighted Cox proportional-hazards models to test the associations of the GRS, obesity and lifestyle score with incident type 2 diabetes, as well as the interactions of the GRS with obesity and unfavourable lifestyle in relation to incident type 2 diabetes.

Results Obesity (BMI ≥ 30 kg/m^2) and unfavourable lifestyle were associated with higher risk for incident type 2 diabetes regardless of genetic predisposition ($p > 0.05$ for GRS–obesity and GRS–lifestyle interaction). The effect of obesity on type 2 diabetes risk (HR 5.81 [95% CI 5.16, 6.55]) was high, whereas the effects of high genetic risk (HR 2.00 [95% CI 1.76, 2.27]) and unfavourable lifestyle (HR 1.18 [95% CI 1.06, 1.30]) were relatively modest. Even among individuals with low GRS and favourable lifestyle, obesity was associated with a >8-fold risk of type 2 diabetes compared with normal-weight individuals in the same GRS and lifestyle stratum.

Conclusions/interpretation Having normal body weight is crucial in the prevention of type 2 diabetes, regardless of genetic predisposition.

Keywords Body weight · Gene–environment interaction · Genetic risk score · Healthy lifestyle · Obesity · Type 2 diabetes

Theresia M. Schnurr and Hermina Jakupović contributed equally to this work.

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Research in context

What is already known about this subject?

- Type 2 diabetes is a common disease with a rapidly increasing global prevalence that has been largely attributed to the ongoing pandemic of obesity and a sedentary lifestyle
- Lifestyle interventions designed for weight loss through intensive lifestyle counselling have been shown to delay the onset of type 2 diabetes among individuals with impaired glucose tolerance
- The effects of lifestyle behaviours and weight loss on type 2 diabetes risk may vary between individuals depending on genetic variation

What is the key question?

- Are the effects of obesity and unfavourable lifestyle on risk of type 2 diabetes accentuated by genetic predisposition?

What are the new findings?

- Obesity and unfavourable lifestyle are associated with increased risk of incident type 2 diabetes regardless of genetic risk
- The associations of genetic and lifestyle risk scores with incident type 2 diabetes are relatively modest compared with the association of obesity with diabetes risk, underlining the importance of weight management in diabetes prevention

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

- Weight management by healthy lifestyle should be recommended as a prevention strategy for all individuals, regardless of genetic predisposition to type 2 diabetes

Abbreviations

GRS	Genetic risk score
GWAS	Genome-wide association study
MET	Metabolic equivalent of task
ROC	Receiver operating characteristic

Introduction

Type 2 diabetes is a common disease with a rapidly increasing global prevalence that has been largely attributed to the ongoing pandemic of obesity and a sedentary lifestyle [1–3]. Public health strategies to prevent type 2 diabetes focus on weight management and promotion of healthy lifestyles [4, 5]. Lifestyle interventions designed for weight loss through intensive lifestyle counselling have been shown to delay the onset of type 2 diabetes among individuals with impaired glucose tolerance [6, 7]. However, the effects of lifestyle behaviours and weight loss on type 2 diabetes risk may vary between individuals depending on genetic variation [6, 7]. To understand the role of genetic variation in the prevention of type 2 diabetes, it is important to elucidate the interaction between genetic predisposition, obesity and lifestyle behaviours.

Recently, a case-cohort study that examined the joint association of genetic predisposition and unfavourable lifestyle with incident type 2 diabetes in the UK Biobank found that type 2 diabetes risk is increased by >10-fold in individuals with an unfavourable lifestyle, independent of genetic risk [8]. However, unfavourable lifestyle was defined using a multifactorial score that considered obesity as a risk factor equal to smoking behaviour, physical activity and diet. Hence, the study did not allow distinguishing between the effects of obesity and other alterable lifestyle factors in the development of type 2 diabetes. Furthermore, lifestyle recommendations designed for the prevention of cardiovascular disease were applied rather than type 2 diabetes-specific recommendations, and genetic risk was estimated using 38 known type 2 diabetes risk variants rather than ~200 risk variants identified in the most recent genome-wide association study (GWAS) [9].

In the present study, we address these shortcomings by examining the joint association of genetic risk, obesity and unfavourable lifestyle with incident type 2 diabetes within a case-cohort sample of 4729 cases and a randomly selected subcohort of 5402 individuals from Denmark.

Methods

Study population

The present case-cohort study is nested within the Danish Diet, Cancer and Health cohort established in 1993–1997 [10]. Altogether 160,725 native Danish citizens living in the

urban areas of Copenhagen and Aarhus were invited to participate, and 57,053 eligible participants without a previous cancer diagnosis were finally recruited. The study complies with the Declaration of Helsinki and has been approved by the Health Research Ethics, Capital Region of Denmark and the Danish Data Protection Agency. All participants gave written informed consent at inclusion.

The participants were followed up from baseline until the date of the diagnosis of diabetes, death, emigration, date of change of personal identification number, or the end of follow-up on 31 December 2011, whichever came first. Incident cases of type 2 diabetes were identified through the National Diabetes Register, where participants were defined as diabetic if they met one of the following criteria [11–14]: registration with a diabetes diagnosis in the National Patient Register; registration of chiropody (as a diabetic patient); five blood glucose measurements in a one year period or two blood glucose measurements per year in five consecutive years; purchase of prescribed insulin recorded in the National Health Service Register; or purchase of oral glucose-lowering drugs in the Danish National Prescription Registry (electronic supplementary material [ESM] Table 1). Overall, the positive predictive value for the identification of diabetes cases using the criteria was 89%, and the sensitivity was 86% [14].

We genotyped a total of 4771 individuals with incident diabetes diagnosis by 31 December 2011 and a randomly drawn subcohort of 5655 individuals who also included 689 individuals who developed diabetes (due to the random selection). The genotyping was performed using the Illumina Human Core Exome BeadChip (Illumina, San Diego, CA, USA) and genotypes were called using the Illumina BeadStudio algorithm. The genotype data were imputed to the Haplotype Reference Consortium (HRC) reference panel 1.1 on the Michigan server using Minimac3.

We excluded closely related individuals, samples with extreme inbreeding coefficients, mislabelled sex or call rate <95%, duplicates, and individuals identified as ethnic outliers based on genome-wide principal component analysis. As indicated in ESM Fig. 1, we also excluded individuals with type 2 diabetes at baseline and participants that had missing information on lifestyle behaviour or covariates. After the exclusions, a total of 4729 incident type 2 diabetes cases and a randomly selected subcohort of 5402 individuals, of whom 575 developed incident type 2 diabetes, remained in the study population. The median follow-up time was 14.7 years (interquartile range 9.5–15.7 years).

Genetic risk score construction

The SNPs included in the genetic risk score (GRS) were selected based on the most recent DIAMANTE consortium meta-analysis of 32 European-descent GWAS including 74,124 individuals with type 2 diabetes and 824,006 control participants [9]. Of the 231 SNPs that reached the genome-wide significance threshold ($p < 5\times 10^{-8}$) in the BMI-unadjusted primary discovery analysis [9], we included 218 loci with minor allele frequency (MAF) >1% and good imputation quality (INFO > 0.7) in the Diet, Cancer and Health cohort. We excluded all genetic variants ($n = 25$) that had a genome-wide significant association with BMI or were in strong linkage disequilibrium ($r^2 > 0.8$ in 1000 Genomes European panel) with a BMI locus in the largest and most recently published GWAS for BMI [15], except for the strongest known type 2 diabetes risk locus in *TCF7L2* [16]. We constructed a weighted type 2 diabetes risk-increasing GRS consisting of the remaining 193 loci by summing the number of type 2 diabetes-increasing alleles weighted by the OR of the selected SNPs estimated in the discovery GWAS [9]. Information on the SNPs included 25 in the GRS, the risk alleles, risk-allele frequencies, imputation INFO scores, and respective ORs that were used as weights for the calculation of the GRS are presented in ESM Table 2. The GRS was stratified into low (lowest 20%), intermediate and high risk (top 20%) groups.

Assessment of body weight

BMI was calculated from weight and height measured at baseline by dividing body weight in kg by height in metres squared. We defined individuals as normal weight, overweight and obese if they had a BMI <25 kg/m^2, ≥25 – <30 kg/m^2 and ≥ 30 kg/m^2, respectively.

Assessment of lifestyle

We adapted lifestyle intervention guidelines established by an initiative of the Danish Ministry of Health [4] and recommended for type 2 diabetes prevention by the Danish Diabetes Association, to create a multifactorial lifestyle score for type 2 diabetes risk (Table 1). Lifestyle was assessed by first defining dichotomous variables (0/1) for adherence to regular physical activity, healthy dietary pattern, smoking status and moderate alcohol consumption, as described in detail below, where 1 point was given for adherence to each favourable lifestyle behaviour. The points were subsequently summed to calculate a lifestyle score for the combined adherence to favourable lifestyle behaviours, where unfavourable lifestyle was defined as adherence to none or one favourable lifestyle behaviour, intermediate lifestyle as adherence to two favourable lifestyle behaviours, and favourable lifestyle as adherence to three or four favourable lifestyle behaviours.

Physical activity Physical activity was assessed by a previously validated questionnaire [17] that includes questions on walking, cycling, housework, sports, do-it-yourself activities

Table 1 Baseline characteristics of the overall study population and type 2 diabetes cases comprising the 9556 participants included in the present analysis of the Danish Diet, Cancer and Health cohort

Variable	Overall study population, $N = 9556$	Incident type 2 diabetes cases, $n = 4729$
Age (years)	56.1 ± 4.3	56.5 ± 4.4
Female sex	4742 (49.6)	2158 (45.6)
BMI (kg/m^2)	27.1 ± 4.5	28.6 ± 4.7
GRS	214.4 ± 8.6	215.5 ± 8.5
Lifestyle score	2.2 ± 1.0	2.2 ± 1.0
Body-weight status[a]		
Normal weight	3361 (35.2)	988 (20.9)
Overweight	4107 (43.0)	2173 (46.0)
Obese	2088 (21.8)	1568 (33.1)
Educational level[b]		
High (≥10 years)	1845 (19.3)	722 (15.3)
Middle (8–9 years)	4373 (45.8)	2113 (44.7)
Low (≤7 years)	3338 (34.9)	1894 (40.0)
Favourable lifestyle factors		
No current smoking	6123 (64.1)	2930 (62.0)
Regular physical activity	4806 (50.3)	2306 (48.8)
Moderate alcohol consumption	5091 (53.3)	2586 (54.7)
Healthy diet	5043 (52.8)	2421 (51.2)
Lifestyle score[c]		
Favourable lifestyle	3819 (40.0)	1821 (38.5)
Intermediate lifestyle	3312 (34.6)	1651 (34.9)
Unfavourable lifestyle	2425 (25.4)	1257 (26.6)
GRS categories		
Low GRS (Q1)	1912 (20.0)	766 (16.2)
Intermediate GRS (Q2–4)	5732 (60.0)	2863 (60.5)
High GRS (Q5)	1912 (20.0)	1100 (23.3)

Data are presented as *n* (%) or mean ± SD

[a] Normal weight: BMI <25 kg/m^2 ; overweight: ≥25 – <30 kg/m^2 ; obese: BMI ≥ 30 kg/m^2

[b] Estimated by duration of education

[c] Favourable lifestyle: 3 or 4 favourable lifestyle factors; intermediate lifestyle: 2 favourable lifestyle factors; unfavourable lifestyle: 0 or 1 favourable lifestyle factors

Q, quintile

and gardening. As described previously [18], each type of physical activity was assigned a metabolic equivalent of task (MET) estimate according to the compendium of physical activities [19], which allows estimation and classification of the energy costs of different activities based on their rate of energy expenditure. MET min/week were calculated from the median MET of physical activity performed in the summer and winter and multiplied by the number of minutes spent in the activity per week. Individuals were defined as having low or high physical activity levels based on the median 55.0 MET min/week in the study sample.

Dietary pattern The participants completed a 192-item Food Frequency Questionnaire at baseline [20–22]. The intake of specific foods and nutrients was calculated by the FoodCalc software [23]. We adapted the Danish official food-based dietary guidelines that are based on the Nordic Nutrition Recommendations [24] and referred to by the Danish Diabetes Association [25], to calculate a healthy diet index comprising seven items (ESM Table 3). One of the original recommendations, concerning sodium intake, was excluded in the present analyses, due to lack of data on sodium intake in the Diet, Cancer and Health cohort. One point was given for reaching the recommended consumption of fruits and vegetables, whole grains, fish, low-fat (maximum fat content of 1.5%) dairy products, as well as for recommended low consumption of red meat (including unprocessed and processed meat and meat products), saturated fat, and sugar-sweetened beverages or juices (including fruit and vegetable juice). The points were summed to assess adherence to healthy diet (range 0 [no adherence] to 7 [highest adherence]), and a dichotomous healthy diet variable was formed by defining

low adherence as 0 to 2 points and middle to high adherence as 3 to 7 points (Table 1). The cut-off for the healthy diet index was set at three out of seven items to ensure sufficient statistical power, as this value was closest to the median of the study population and thus balanced the sample sizes of the two strata.

Alcohol consumption, smoking and educational level Alcohol consumption was calculated from the 192-item Food Frequency Questionnaire. Based on current Nordic Nutrition Recommendations [24], moderate alcohol consumption was defined as ≤6 units/week for women and ≤12 units/week for men, and high alcohol consumption as >6 units/week for women and >12 units/week for men, where 1 unit is equivalent to 12 g of pure alcohol. Information on smoking habit (current smoker, non-smoker) and educational level defined by its duration (≤7, 8–9, and ≥10 years) [26, 27] was obtained from the baseline questionnaire.

Statistical analysis

We used Prentice-weighted Cox proportional-hazards models using the 'cch' command integrated into the R package 'survival' to test the associations of GRS, obesity and lifestyle score with incident type 2 diabetes, as well as the interactions of the GRS with obesity and unfavourable lifestyle in relation to incident type 2 diabetes. Consistent with previous studies [8, 28], we determined whether participants had a low (quintile 1), intermediate (quintiles 2 to 4) or high (quintile 5) genetic risk for type 2 diabetes and a favourable (3 or 4 favourable lifestyle factors), intermediate (2 favourable lifestyle factors) or an unfavourable lifestyle (0 or 1 favourable lifestyle factors). All analyses were adjusted for age at baseline, sex and educational level. The analyses including the GRS were additionally adjusted for the first three genome-wide principal components to correct for population stratification. Analyses including the GRS and lifestyle score were performed with and without adjustment for BMI. All analyses were performed using RStudio software, version 3.3.1 (2016-06-21; Boston, MA, USA).

Power calculations and assessment of predictive utility of the models We performed power calculations through 2000 simulation analyses using the simplified approximating setting of logistic regression, hence modelling the odds of incident diabetes (being a case vs a non-case) during the follow-up. The GRS*BMI setting was mimicked using estimated variables from a corresponding fitted model while adjusting for sex and age. We derived the least detectable interaction effect based on the current sample size ($n = 9556$), significance level 5% and 80% power. The power calculations were performed in Stata 15.1 (StataCorp, College Station, TX, USA; www.stata.com). We also assessed the predictive performance of BMI, the lifestyle score and the genetic risk score for incident type 2 diabetes by performing a receiver operating characteristic (ROC) analysis (ESM Table 4).

Results

Population characteristics

The baseline characteristics of the 4726 individuals with type 2 diabetes and the randomly selected subcohort of 5402 participants included in the presented analyses are provided in Table 1. The mean age of all participants was 56.1 years (range 50–65) and 49.6% were women. Overall, 40.0% of all participants had a favourable lifestyle, 34.6% had an intermediate lifestyle and 25.4% had an unfavourable lifestyle, and 21.8% were classified as obese, 43.0% as overweight and 35.2% as having normal weight.

Associations of the GRS, obesity and lifestyle with incident type 2 diabetes

As provided in ESM Table 5, participants with high or intermediate genetic risk had an HR of 2.00 (95% CI 1.76, 2.27) or an HR of 1.49 (95% CI 1.34, 1.66) for incident type 2 diabetes, respectively, compared with individuals with low genetic risk. Participants with an unfavourable or intermediate lifestyle had an HR of 1.18 (95% CI 1.06, 1.30) or an HR of 1.10 (95% CI 1.00, 1.20) for incident type 2 diabetes, respectively, compared with participants with a favourable lifestyle. Individuals who were overweight or obese had an HR of 2.37 (95% CI 2.15, 2.62) or an HR of 5.81 (95% CI 5.16, 6.55) for higher risk of incident type 2 diabetes, respectively, than individuals with normal body weight. In sensitivity analyses that excluded 62 individuals who were underweight (BMI < 18.5 kg/m^2), the associations of being overweight and obese with type 2 diabetes risk remained virtually unchanged (HR 2.38 [95% CI 2.16, 2.62] and HR 5.82 [95% CI 5.17, 6.56], respectively).

The associations of high genetic risk and unfavourable lifestyle with type 2 diabetes risk remained similar after adjustment for BMI (HR 2.15 [95% CI 1.85, 2.50] and HR 1.29 [95% CI 1.15, 1.43], respectively), suggesting that the associations of GRS and unfavourable lifestyle with type 2 diabetes were not mediated by BMI.

Interaction of the GRS with obesity and lifestyle on incident type 2 diabetes

There was no significant interaction between the GRS and continuous BMI ($p = 0.35$) or the lifestyle score ($p = 0.72$) on incident type 2 diabetes (ESM Table 6); higher BMI and

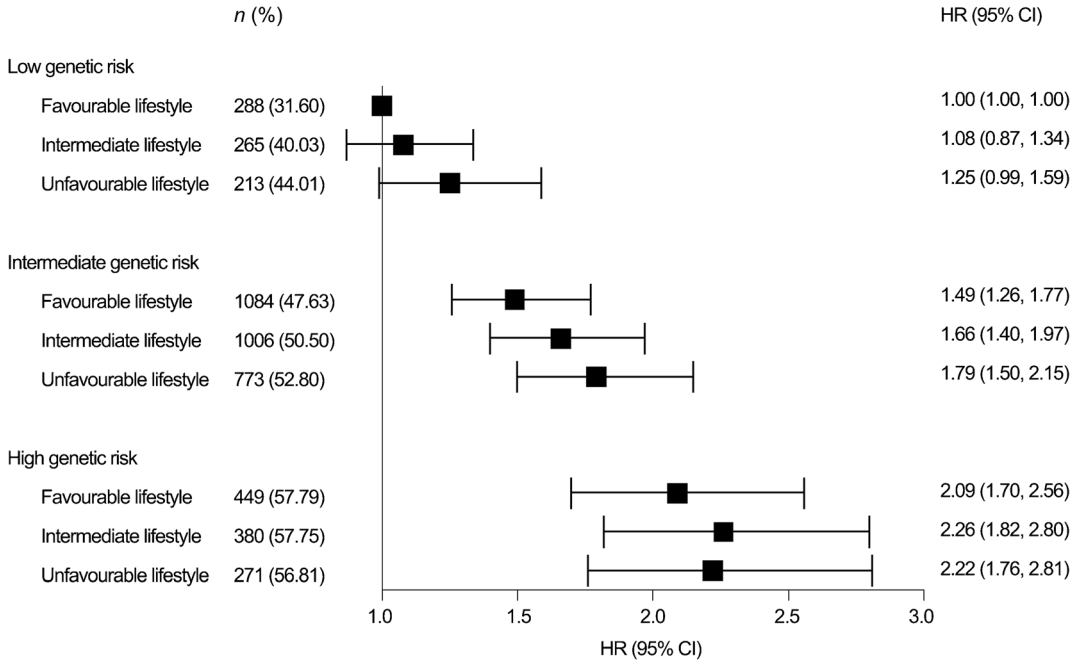

Fig. 1 Associations of GRS and lifestyle with incident type 2 diabetes. Analyses were adjusted for age, sex, educational level and the first three genome-wide principal components. *n*, number of incident type 2 diabetes cases

unfavourable lifestyle were similarly associated with increased risk of type 2 diabetes across all genetic risk groups (Figs 1 and 2). We also did not find significant interactions between the GRS and the four individual lifestyle components comprising the lifestyle score on the risk of type 2 diabetes (ESM Table 7). In a sensitivity analysis excluding 62 individuals who were underweight (BMI < 18.5 kg/m^2), the interaction between the GRS and continuous BMI on incident type 2 diabetes ($p = 0.49$) remained virtually unchanged (ESM Fig. 2).

Through power calculation, we estimated that the least detectable GRS*BMI interaction effect that could be detected in the present sample with significance level 0.05 and 80% power is OR = 1.0025.

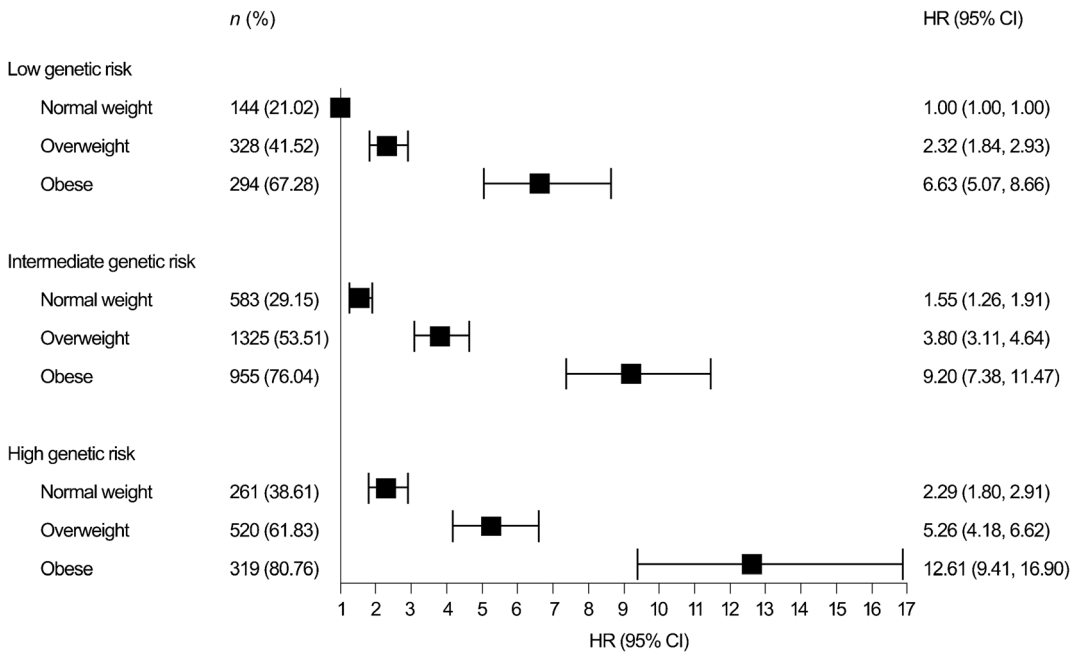

Fig. 2 Associations of GRS and body-weight status with incident type 2 diabetes. Analyses were adjusted for age, sex, educational level and the first three genome-wide principal components. *n*, number of incident type 2 diabetes cases

Table 2 Combined associations of GRS, lifestyle and body-weight status with incident type 2 diabetes

GRS category stratified by body-weight status	Lifestyle score					
	Favourable lifestyle		Intermediate lifestyle		Unfavourable lifestyle	
	HR (95% CI)	n_{cases} (%)	HR (95% CI)	n_{cases} (%)	HR (95% CI)	n_{cases} (%)
Low GRS						
Normal weight	1.00 (Ref.)	45 (16.4)	1.49 (0.96, 2.31)	57 (23.6)	1.61 (1.00, 2.59)	42 (24.9)
Overweight	2.79 (1.88, 4.13)	125 (39.7)	3.08 (2.07, 4.60)	116 (41.3)	3.57 (2.33, 5.47)	88 (45.4)
Obese	8.44 (5.43, 13.14)	119 (67.2)	8.20 (5.14, 13.08)	92 (66.2)	9.94 (6.09, 16.23)	83 (68.6)
Intermediate GRS						
Normal weight	1.67 (1.17, 2.40)	191 (25.0)	2.04 (1.43, 2.93)	201 (29.5)	2.60 (1.80, 3.74)	191 (34.4)
Overweight	4.54 (3.22, 6.40)	503 (51.4)	5.09 (3.59, 7.20)	471 (53.2)	5.81 (4.06, 8.32)	351 (57.4)
Obese	10.78 (7.45, 15.58)	390 (73.2)	13.43 (9.16, 19.70)	334 (78.6)	13.09 (8.72, 19.66)	231 (77.5)
High GRS						
Normal weight	2.84 (1.89, 4.27)	99 (38.4)	3.25 (2.14, 4.95)	88 (39.1)	2.97 (1.93, 4.59)	74 (38.3)
Overweight	6.31 (4.30, 9.26)	211 (60.8)	6.46 (4.36, 9.58)	176 (61.1)	9.41 (6.09, 14.54)	133 (66.2)
Obese	15.71 (9.86, 25.05)	139 (80.8)	19.64 (11.86, 32.50)	116 (82.9)	14.54 (8.09, 26.13)	64 (77.1)

Analyses were adjusted for age, sex, educational level and the first three genome-wide principal components

Ref., reference

Combined association of the GRS, obesity and lifestyle with incident type 2 diabetes

Individuals who ranked high for all three risk factors, with obesity, high GRS and unfavourable lifestyle, had an HR of 14.54 (95% CI 8.09, 26.13) for incident type 2 diabetes, compared with normal-weight, individuals low GRS and favourable lifestyle. Notably, even among individuals with low GRS and favourable lifestyle, obesity was strongly associated with higher type 2 diabetes risk with an HR of 8.44 (95% CI 5.43, 13.14) compared with normal weight individuals in the same GRS and lifestyle stratum (Table 2). ROC analyses suggested that the GRS and the lifestyle score have very little predictive utility (AUC = 72.85 and 72.05, respectively) on top of BMI, age and sex (AUC = 71.81).

Discussion

In the present study, we found that obesity and unfavourable lifestyle are associated with increased risk of incident type 2 diabetes regardless of genetic risk. We also found that the associations of the GRS and lifestyle score with risk of incident type 2 diabetes are relatively modest compared with the association of obesity with diabetes risk, underscoring the importance of weight management in diabetes prevention.

Our results show that there was no significant interaction between behavioural lifestyle and genetic risk of type 2 diabetes. An unfavourable lifestyle was associated with similar increase in relative type 2 diabetes risk across each stratum of genetic risk. These findings are consistent with previous studies within the InterAct Consortium [29] and the UK Biobank [8]. Overall, the results indicate that a favourable lifestyle should be universally recommended in the prevention of type 2 diabetes, regardless of genetic predisposition, thus supporting current public health guidelines. The study within UK Biobank investigated the effect of a lifestyle score on genetically determined type 2 diabetes risk, finding that a poor lifestyle is associated with a >10-fold increased risk of incident type 2 diabetes, even in individuals with a low genetic risk [8]. However, the study incorporated being overweight/obese as one component of the multifactorial lifestyle score, which did not allow distinguishing between the effects specific to obesity and other lifestyle factors on type 2 diabetes risk. In the present study, we showed that the association with incident type 2 diabetes is dominated by obesity over the impact of unfavourable lifestyle, with a >8-fold risk of type 2 diabetes found for individuals who were obese, despite a favourable lifestyle.

We found no significant interaction between the GRS and BMI in relation to the risk of incident type 2 diabetes. In contrast, a previous analysis within the InterAct Consortium reported that the effect of a GRS for type 2 diabetes (based on 49 established type 2 diabetes loci) on diabetes risk is modified by BMI, such that the effect of the GRS is significantly greater among individuals who are leaner at baseline [29]. It is possible that the present analyses were underpowered to detect an interaction between the GRS and BMI. Alternatively, the inclusion of >150 additional recently identified type 2 diabetes risk variants in the GRS used in the present analyses may have

incorporated a larger number of genetic loci that have an equal effect between lean and obese individuals, whereas the earlier discovered loci may have included a relatively larger proportion of variants with primary effects on insulin secretion and a larger effect in lean individuals, due to the exclusion of obese individuals in early GWAS for type 2 diabetes [30]. Indeed, a BMI-stratified analysis, published in 2012, showed a larger OR in normal-weight individuals compared with individuals who were obese for 29 of 36 diabetes loci known at the time [31]. The InterAct Consortium also did not exclude known obesity risk variants when constructing the GRS, which could lead to spurious interactions between the GRS and BMI due to gene–environment dependence [32].

Strengths of the present study are the large number of incident type 2 diabetes cases, retrieved objectively from the Danish Diabetes Registry, and the long follow-up period. Information on lifestyle was collected before type 2 diabetes diagnosis, which ensures that recall bias did not influence the present results. Furthermore, we comprised a lifestyle score specific for type 2 diabetes and took advantage of ~200 loci recently identified to be associated with type 2 diabetes [9]. As a limitation, the present analyses were performed in a population of European genetic ancestry and cannot immediately be generalised to other ancestry groups.

To conclude, we found that individuals with obesity and an unfavourable lifestyle are at greater risk of incident type 2 diabetes regardless of their genetic risk. The results suggest that type 2 diabetes prevention by weight management and healthy lifestyle is critical across all genetic risk groups. Furthermore, we found that the effect of obesity on type 2 diabetes risk is dominant over other risk factors, highlighting the importance of weight management in type 2 diabetes prevention.

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Data availability Due to restrictions related to Danish law and protecting patient privacy, the combined set of data as used in this study can only be made available through a trusted third party, Statistics Denmark. This state organisation holds the data used for this study. University-based Danish scientific organisations can be authorised to work with data within Statistics Denmark and such organisations can provide access to individual scientists inside and outside of Denmark. Requests for data may be sent to Statistics Denmark (www.dst.dk/en/kontakt) or the Danish Data Protection Agency (www.datatilsynet.dk/english).

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Contribution statement The research initiative and study concept were taken and designed by OP and TOK. TMS, HJ and TOK designed the present analysis. TMS, HJ and LÄ performed statistical analysis. TMS, HJ and TOK interpreted the data and drafted the manuscript. AT and KO collected data and contributed to discussions. GDC, NG, TIAS, OP and TH contributed to discussions. All authors interpreted the results, edited and revised the manuscript and read and approved the final version of the manuscript. TMS and HJ are the guarantors of the work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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