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Genetic susceptibility, obesity and lifetime risk of type 2 diabetes: The ARIC study and Rotterdam Study

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Abstract

Aims: Both lifestyle factors and genetic background contribute to the development of type 2 diabetes. Estimation of the lifetime risk of diabetes based on genetic information has not been presented, and the extent to which a normal body weight can offset a high lifetime genetic risk is unknown.

Methods: We used data from 15,671 diabetes-free participants of European ancestry aged 45 years and older from the prospective population-based ARIC study and Rotterdam Study (RS). We quantified the remaining lifetime risk of diabetes stratified by genetic risk and quantified the effect of normal weight in terms of relative and lifetime risks in low, intermediate and high genetic risk.

Results: At age 45 years, the lifetime risk of type 2 diabetes in ARIC in the low, intermediate and high genetic risk category was 33.2%, 41.3% and 47.2%, and in RS 22.8%, 30.6% and 35.5% respectively. The absolute lifetime risk for individuals with normal weight compared to individuals with obesity was 24% lower in ARIC and

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8.6% lower in RS in the low genetic risk group, 36.3% lower in ARIC and 31.3% lower in RS in the intermediate genetic risk group, and 25.0% lower in ARIC and 29.4% lower in RS in the high genetic risk group.

Conclusions: Genetic variants for type 2 diabetes have value in estimating the lifetime risk of type 2 diabetes. Normal weight mitigates partly the deleterious effect of high genetic risk.

KEYWORDS

BMI, lifetime risk, obesity, polygenic score, type 2 diabetes

1 | INTRODUCTION

The burden of type 2 diabetes continues to be a global health crisis and is expected to increase in coming years.[1] Early prevention of diabetes risk factors in adulthood remains crucial for reducing the impact of diabetes on our society.[2] Lifestyle interventions successfully delay onset of type 2 diabetes,[3,4] particularly in individuals at high risk.[4] Efficient prevention strategies require proper identification of individuals with increased risk of disease over the course of their lifetime.

Type 2 diabetes is caused by both genetic and environmental risk factors. In recent years, genome-wide association studies (GWAS) have identified multiple common genetic risk variants for type 2 diabetes.[5] Studies additionally show that genetic variation may predict incidence of type 2 diabetes,[6-12] and that lifestyle intervention preventing obesity may mitigate high genetic risk.[13-16] These previous reports utilizing genetic information to predict diabetes have limited follow-up time, for example, 10 years. The value of genetic information in lifetime risk assessment of type 2 diabetes has not been reported. Previously, we characterized the lifetime risk of full range of glucose impairments, from

Novelty Statement:

What is known?

- Type 2 diabetes has both genetic and environmental causes.

What we found?

- High genetic risk of type 2 diabetes is associated with high lifetime risk of the disease.
- Genetic predisposition for type 2 diabetes risk can be offset by maintaining a normal weight.

What are the implications of the study?

- Genetic risk should be considered when evaluating the lifetime risk of type 2 diabetes, which may play an important role in guiding early lifestyle interventions particularly for individuals a with a high genetic risk and high BMI.

normoglycaemia to prediabetes, type 2 diabetes and eventual insulin use.[17] This work highlighted the important influence of BMI and waist circumference on lifetime risk. The absolute effect of BMI on genetic lifetime risk has not been published.

We hypothesized that genetic information can be utilized to predict the lifetime risk of type 2 diabetes and that adherence to a normal weight mitigates high genetic risk. To this end, we used data from two prospective population-based cohort studies, the Atherosclerosis Risk in Communities (ARIC) study and the Rotterdam Study (RS), to estimate the lifetime risk of diabetes in individuals at low, intermediate and high genetic risk, based on a polygenic score of 403 common DNA sequence variants so far identified for type 2 diabetes.[5] Additionally, we investigated whether normal body weight mitigates a high genetic lifetime risk of type 2 diabetes.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study samples

The ARIC study is a population-based prospective cohort study of cardiovascular disease and subsequent risk factors sponsored by the National Heart, Lung, and Blood Institute (NHLBI). ARIC included 15,792 individuals, predominantly European American and African American, aged 45 to 64 years at baseline (1987–89), chosen by probability sampling from four US communities. Cohort members completed three additional triennial follow-up examinations, a fifth exam in 2011–2013, a sixth exam in 2016–2017 and a seventh exam in 2018–2019. The ARIC study has been described in detail previously.[18] In total, 8,243 ARIC participants of European ancestry had genetic data available and were free of type 2 diabetes at baseline examination. Data from six in-person examinations, supplemented by interim telephone interviews were available for this analysis. The ARIC study has been approved by the Institutional Review Board at all participating institutions. All participants provided written informed consent.

The RS is a prospective population-based cohort study among individuals 45 years and older in Rotterdam, the Netherlands.[19] The study commenced in 1990 when all inhabitants aged 55 years and older of a well-defined area in the city of Rotterdam were invited, of whom 7,985 participated. In 2000, the study was extended with a second cohort of 3,011 inhabitants that had reached the age of 55 or had moved into the study area after the start of the first cohort. Similarly, a third cohort enrolled 3,932 participants aged 45 years and older in 2006. There were no eligibility criteria to enter the RS except minimum age and postal code. The third centre visit of the first cohort (1997–1999), and the first centre visit of the second (2000–2001) and third (2006–2008) cohort were used as baseline for this analysis. In total, 7,428 participants without diabetes at baseline had genetic data available and were included in the analysis. The RS has been approved by the Medical Ethics Committee of the Erasmus MC according to the 'Population Screening Act: Rotterdam Study', executed by the Ministry of Health, Welfare, and Sports of the Netherlands. All participants provided written informed consent.

2.2 | Diabetes diagnosis

Type 2 diabetes was defined according to the WHO guidelines as a fasting serum glucose of 7.0 mmol/L or higher, a non-fasting serum glucose of 11.0 mmol/L or higher (when fasting sample was not available), or the use blood glucose lowering medication.

For the ARIC study, cases were ascertained at baseline and during research visits using glucose measurements, self-reported diagnosis of type 2 diabetes by a physician or self-reported use of diabetes medication. A physician diagnosis or use of diabetic medication that occurred between visits was self-reported at annual or semi-annual structured telephone interviews.

In the RS, cases of type 2 diabetes were ascertained at baseline and during follow-up by use of general practitioners' records, hospital discharge letters and serum glucose measurements from the research centre visits, which take place every 4 years. Information about the use of glucose-lowering medication was obtained from both structural home interviews and linkage to local pharmacy dispensing records. Two research physicians independently classify information on occurrence, certainty, and date of onset of all potential diabetes diagnoses following the WHO guidelines. A diabetologist reviewed cases where consensus could not be reached between the research physicians. The diabetologist´s judgment is considered decisive.

2.3 | Risk factors

Risk factors for diabetes were selected based on the prediction analysis from the manuscript by Wilson et al.[20] In the ARIC and RS, body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. For BMI, participants were classified into three categories: <25 kg/m^2 (normal weight), ≥25 and <30 kg/m^2 (overweight) and ≥30 kg/m^2 (obesity). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, glucose and triglycerides were measured using standard laboratory techniques. Smoking was categorized as current, former or never. Hypertension

was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg or the use of blood pressure lowering medication. Information on smoking behaviour was assessed in both studies through structured in-person interviews. In the ARIC study, medication use was self-reported during the interview process. In the RS, medication use was additionally established using local pharmacy dispensing records.

2.4 | Genotyping and polygenic score

ARIC participants were genotyped using the Affymetrix 6.0 array (Affymetrix Inc). Genotyping in the RS was done using the Illumina 550K and 610K quad array (Illumina Inc). Genotyped variants were imputed to the Haplotype Reference Consortium (r1.1 2016).[21] Haplotype phasing and imputation was performed using the Michigan Imputation Server, which is available at https://imputationserver.sph.umich.edu.

A recent GWAS based on individuals of European ancestry identified 403 independent genetic variants associated with type 2 diabetes.[5] Using the 403 genetic variants identified in this study, we created weighted polygenic score by multiplying the risk allele dosage with the effect estimates reported in the GWAS of type 2 diabetes. An additive weighted polygenic score was calculated by summing the weighted dosages for each individual.[22] Separately in ARIC and the RS, all individuals were categorized into low (quintile 1), intermediate (quintiles 2–4) and high (quintile 5) genetic risk categories, with the low genetic risk category as the reference.

2.5 | Statistical analysis

Individual baseline characteristics were reported according to low, intermediate and high genetic risk categories. Significant differences between groups within studies were determined using ANOVA and Kruskal–Wallis tests for normal and non-normal distributed continuous data, respectively, and χ^2 tests for categorical data.

The association between genetic risk category and incident type 2 diabetes was assessed using Fine and Gray proportional hazards models accounting for the competing risk of death.[23] Model 1 adjusted for age, sex and study sub-cohort (RS) or centre (ARIC study). Model 2 included the same covariates as model 1 along with BMI, systolic blood pressure, HDL cholesterol, triglycerides and smoking status (current, former and never). Model 3 included the same covariates as Model 2, but also included a multiplicative interaction term between BMI and the polygenic score. We tested for violation of the proportional hazard assumption using the scaled Schoenfeld residuals and there was no evidence of violation of the proportional hazard assumption in both cohort studies. Hazard ratios and 95% confidence intervals were reported for each model. Additionally, we estimated the relative risk using normal weight as the reference compared to overweight and obesity in the overall study population and within the genetic risk categories, adjusted for the same covariates as Model 2 excluding BMI.

Remaining lifetime risks for new-onset type 2 diabetes were calculated at different ages using a modified version of survival analysis, taking into account left- and right censoring, and the competing risk of death free of diabetes.[24,25] We calculated lifetime risks at the age of 45, 55, 65 and 75 years, and stratified by low, intermediate and high genetic risk. Additionally, for the age of 45, we calculated the remaining lifetime risk of type 2 diabetes in each polygenic score category, stratified by baseline BMI category.

All P-values were two sided and a significance threshold of $p < 0.05$ was used. All data were analysed using the IBM SPSS Statistics version 21.0.0.1 (IBM Corp) and R version 2.1 with the 'etm' and 'survival' packages.

3 | RESULTS

3.1 | Characteristics of the participants, genetic score and diabetes incidence

Participant baseline characteristics in the ARIC study (n = 8,243) and RS (n = 7428) stratified by low, intermediate and high genetic risk are shown in Table 1. In both cohorts, fasting glucose levels increased across genetic risk strata. Distributions of the genetic score were similar in both studies and are depicted in Figure S1.

In the ARIC study, the median follow-up time was 19.4 years (interquartile interval 9.7–27.0). During a total of 149,639 person-years of follow-up, 2,553 (31%) participants were diagnosed with type 2 diabetes: 388 (24%) in the low genetic risk category, 1,540 (31%) in the intermediate genetic category and 625 (38%) in the high genetic risk category. A total of 2,596 (31%) participants died free of diabetes: 559 (34%) at low genetic risk, 1,562 (32%) at intermediate genetic risk and 475 (29%) at high genetic risk. In the RS, the median follow-up time was 6.9 years (4.3–11.6). During a total of 58,376 person-years of follow-up, 674 (9%) participants were diagnosed with type 2 diabetes: 97 (7%) in the low genetic risk category, 409 (9%) in the intermediate genetic category and 168 (11%) in the high genetic risk category. A total of 1,457 (20%) participants died free of diabetes: 278 (19%) at low genetic risk, 880 (20%) at intermediate genetic risk and 299 (20%) at high genetic risk.

In the ARIC study, the overall diabetes incidence rate was 17.0 per 1,000 person-years (95%CI 16.4–17.7) and the overall mortality rate free of diabetes was 17.3 per 1,000 person-years (95%CI 16.6–18.0). In the RS, the overall diabetes

TABLE 1 Characteristics of the study population, stratified by low, intermediate and high type 2 diabetes genetic risk

	ARIC study			Rotterdam study		
	Type 2 diabetes genetic risk category			Type 2 diabetes genetic risk category		
Characteristics	Low (n = 1649)	Intermediate (n = 4945)	High (n = 1649)	Low (n = 1486)	Intermediate (n = 4456)	High (n = 1486)
Women (n, %)	793 (48.1)	2273 (46.0)	761 (46.1)	847 (57.0)	2549 (57.2)	884 (59.5)
Age (y)	54.2 ± 5.8	54.2 ± 5.6	53.9 ± 5.7	65.0 ± 9.7	64.9 ± 9.7	64.7 ± 9.6
Body mass index (kg/m^2)	26.6 ± 4.5	26.7 ± 4.6	26.7 ± 4.7	27.0 ± 4.0	27.0 ± 4.1	26.9 ± 3.9
Total cholesterol (mmol/L)	5.6 ± 1.1	5.5 ± 1.0	5.6 ± 1.0	5.8 ± 1.0	5.8 ± 1.0	5.7 ± 1.0
HDL cholesterol (mmol/L)	1.3 (1–1.6)	1.3 (1–1.6)	1.2 (1–1.5)	1.4 (1.2–1.7)	1.4 (1.2–1.7)	1.4 (1.1–1.6)
Triglycerides (mmol/L)[a]	1.2 (0.9–1.7)	1.3 (0.9–1.8)	1.3 (0.9–1.8)	1.3 (1.0–1.8)	1.3 (1.0–1.7)	1.3 (1.0–1.8)
Glucose (mmol/L)[a]	5.3 (5.1–5.7)	5.4 (5.1–5.8)	5.5 (5.2–5.9)	5.3 (5.0–5.7)	5.4 (5.1–5.8)	5.5 (5.1–5.9)
Systolic blood pressure (mmHg)	117 ± 16.3	118 ± 16.7	118 ± 16.5	138 ± 20	139 ± 21	139 ± 20
Diastolic blood pressure (mmHg)	71.2 ± 9.9	71.5 ± 10.1	71.6 ± 9.8	79 ± 11	78 ± 11	79 ± 12
Hypertension (n, %)	386 (23.4)	1219 (24.6)	506 (30.7)	732 (50.0)	2156 (48.8)	749 (50.9)
Use of blood pressure lowering drugs (n, %)	470 (28.5)	929 (18.7)	491 (29.8)	286 (20.0)	922 (21.4)	357 (24.7)
Use of lipid lowering agents (n, %)	77 (4.6)	122 (2.5)	61 (3.6)	181 (12.6)	641 (14.8)	261 (18.0)
Current smoking (n, %)	393 (23.8)	1249 (25.3)	418 (25.3)	142 (9.6)	436 (9.8)	141 (9.5)
Former smoking (n, %)	584 (354)	1736 (35.1)	571 (34.6)	583 (39.2)	1706 (38.2)	546 (36.7)
Polygenic score, weighted	24.7 ± 0.3	25.6 ± 0.3	26.6 ± 0.3	24.6 ± 0.4	25.6 ± 0.3	26.6 ± 0.3

Values are mean ±standard deviation or median (interquartile interval) for characteristics with skewed distributions. HDL denotes high-density lipoprotein.
aOnly fasting samples.

incidence rate was 11.5 per 1,000 person-years (95%CI 10.7–12.4) and the overall mortality rate free of diabetes was 25.0 per 1,000 person-years (95%CI 23.8–26.3).

3.2 | Polygenic score, obesity and relative risk of diabetes

Participants in the intermediate and high genetic risk category had a significantly increased risk of type 2 diabetes compared to participants in the low genetic risk category (Table 2). Among participants at high genetic risk, the risk of type 2 diabetes was almost twofold higher compared to those at low genetic risk. We observed a similar trend in risk of diabetes across categories of BMI. Participants with obesity had a more than twofold increased risk of diabetes compared to individuals with a normal weight.

Participants with a normal body weight had lower risk of diabetes compared to participants with overweight and obesity in the intermediate and high genetic risk categories (Figure 1). There was no evidence for multiplicative interaction between the continuous polygenic score and continuous BMI on the risk of type 2 diabetes (ARIC study $p = 0.57$ and RS $p = 0.13$). Among participants at high genetic risk, normal weight was associated with a 56% lower risk of diabetes in the ARIC study, and 55% lower risk in the RS, as compared to obesity.

3.3 | Polygenic score, obesity and remaining lifetime risk of incident type 2 diabetes

In the RS, the remaining lifetime risk of type 2 diabetes among individuals aged 45 years was 22.8% (95% CI 18.4–27.3) in the low genetic risk category, 30.6% (95% CI 27.9–33.4) in the intermediate genetic risk category and 35.5% (95% CI 30.6–40.5) in the high genetic risk category (Table S1). A similar pattern in the lifetime risk of diabetes was observed in ARIC: 32.6% (95% CI 27.8–37.4) in the low genetic risk category, 41.1% (95% CI 38.9–43.2) in the intermediate genetic risk category and 47.6% (95% CI 44.3–50.8) in the high genetic risk category (Table S1). Remaining lifetime risks attenuated with advancing age. Yet, lifetime risks were higher in the high genetic risk category compared to the low genetic risk category at all index ages. Figure 2 depicts the cumulative incidence function in both the ARIC study and RS for participants aged 45 years at low, intermediate and

TABLE 2 Relative risk of type 2 diabetes across genetic risk and body mass index categories

	Cases / Total n	Model 1 Hazard ratio (95%CI)	*p*-value	Model 2 Hazard ratio (95%CI)	*p*-value
ARIC					
Genetic type 2 diabetes risk					
Low	388/1649	reference		reference	
Intermediate	1540/4945	1.45 (1.30– 1.61)	<0·001	1.39 (1.24– 1.55)	<0.001
High	625/1649	1.83 (1.61– 2.07)	<0.001	1.75 (1.54– 1.99)	<0.001
Body mass index					
Normal weight	627/3250	reference		reference	
Overweight	1122/3332	1.96 (1.77– 2.16)	<0.001	1.65 (1.49– 1.83)	<0.001
Obese	804/1652	3.45 (3.10– 3.84)	<0.001	2.52 (2.24– 2.83)	<0.001
Rotterdam Study					
Genetic type 2 diabetes risk					
Low	97 / 1486	reference		reference	
Intermediate	409 / 4456	1.45 (1.16–1.81)	0.001	1.46 (1.17–1.83)	<0.001
High	168 / 1486	1.86 (1.45–2.38)	<0.001	1.91 (1.48–2.45)	<0.001
Body mass index					
Normal weight	131 / 2476	reference		reference	
Overweight	353 / 3540	1.90 (1.55–2.32)	<0.001	1.61 (1.32–1.97)	<0.001
Obese	190 / 1412	2.90 (2.32–3.63)	<0.001	2.22 (1.76–2.79)	<0.001

Model 1 is adjusted for age, sex, and study sub-cohort/research centre. Model 2 is additionally adjusted for systolic blood pressure, high-density lipoprotein cholesterol, triglycerides, smoking and body mass index (in the genetic risk association).

Genetic risk is defined as low (quintile 1 of the weighted polygenic score), intermediate (quintile 2–4), and high (quintile 5).

Normal weight is defined as a body mass index <25 kg/m^2, overweight ≥25 and <30 kg/m^2 and obese ≥30 kg/m^2.

high genetic risk, adjusted for the competing risk of death free of diabetes.

Stratification of individuals at low, intermediate and high genetic risk by BMI category revealed the highest lifetime risk for individuals with obesity at high genetic risk: 59.7% (95%CI 53.3–66.1) in ARIC and 55.3% (95%CI 43.8–66.8) in the RS (Figure 3, Table S2). The lowest lifetime risk was for individuals with a normal weight at low genetic risk (ARIC study 23.8% (95%CI 14.6–33.0) and RS 16.8% (95%CI 9.9–23.7)). Among individuals at high genetic risk, those with a normal weight conferred an absolute more than 25% lower lifetime risk of diabetes compared to their counterparts with obesity (ARIC 34.4 vs. 59.9% and RS 25.9 vs. 55.3%,).

4 | DISCUSSION

In two community-dwelling populations of individuals aged 45 years and older, we observe that a high genetic risk of type 2 diabetes is associated with an almost twofold higher risk of incident type 2 diabetes compared to individuals at low genetic risk, independent from other established diabetes risk factors including BMI. Individuals with a normal weight had a substantial lower lifetime risk of diabetes compared to their counterparts with obesity, particularly in individuals at high genetic risk. This indicates that normal weight may partially mitigate high genetic lifetime risk for type 2 diabetes. From the data we conclude that genetic information may be utilized for lifetime risk prediction, and that preventing obesity is key in type 2 diabetes prevention.

The finding that genetic information contributes to type 2 diabetes risk assessment is in line with previous studies.[6–12,26]. Previous reports limit the prediction of type 2 diabetes to a restricted 10-year time-period as opposed to the remaining lifetime risk of type 2 diabetes. Individuals prefer risk communication in long-term absolute risks.[27] Genetic risk factors affect the risk of disease from birth through the end of life. Therefore, it is of particular interest to study the lifetime risk of type 2 diabetes based on genetic information. In the current study, we are the first to determine the remaining lifetime risk of type 2 diabetes based on genetic risk. Our data suggest that genetic information predicts the lifetime risk of type 2 diabetes and thus may be used to select high-risk individuals early in life that may benefit from intensified lifestyle counselling, even when clinical risk factors are not yet apparent. However, in agreement with findings from earlier reports,[26] the high lifetime risk of type 2 diabetes in individuals with obesity at all genetic risk strata highlights the importance of lifestyle interventions that maintain a normal weight, and from a public

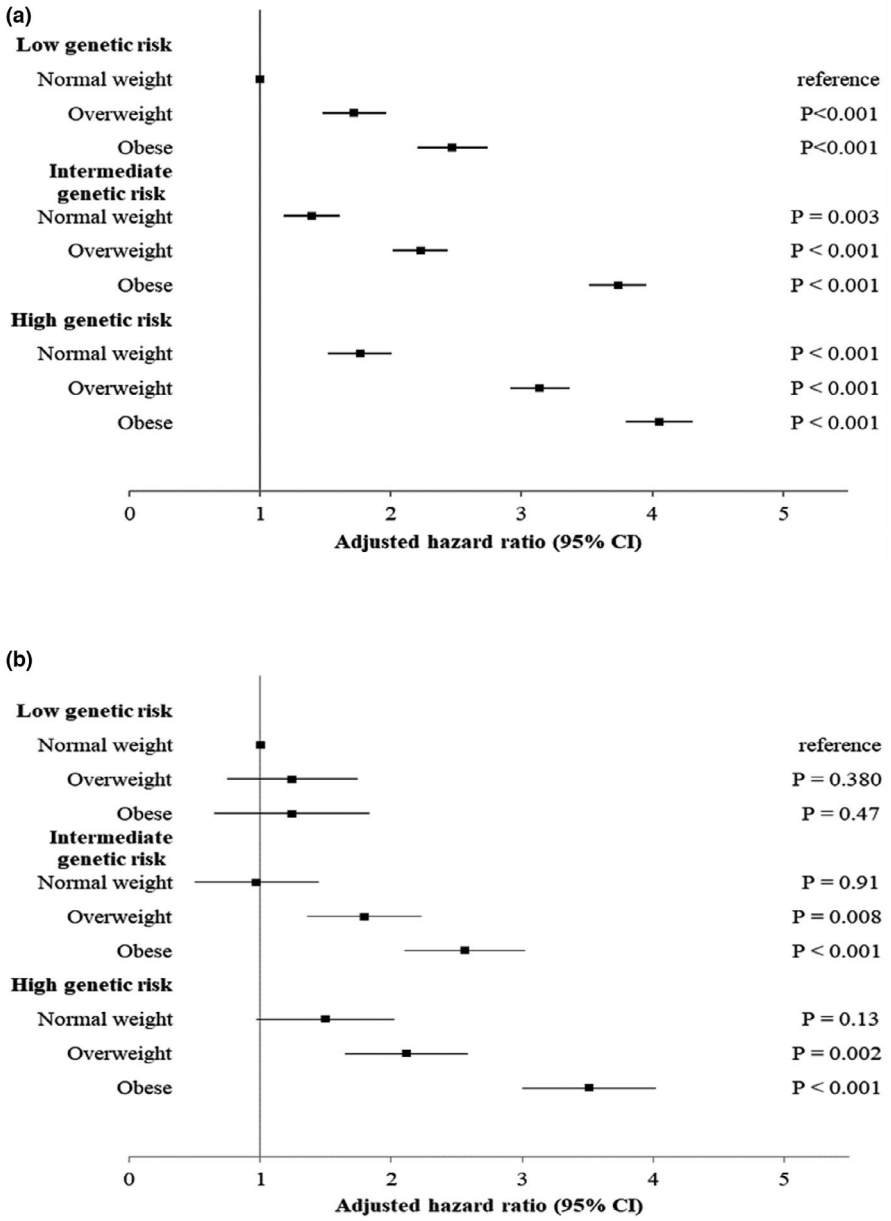

FIGURE 1 Risk of incident type 2 diabetes according to genetic susceptibility and body mass index in the ARIC study (A) and Rotterdam Study (B). Presented are the hazard ratios for incident type 2 diabetes according to the genetic and body mass index risk, adjusted for age, sex, systolic blood pressure, HDL cholesterol, triglycerides, smoking status and study subcohort/research centre. Participants with low genetic risk and a normal weight are the reference group

health intervention perspective, it would therefore be logical to focus at older ages on individuals with obesity.

In primordial prevention of type 2 diabetes, maintaining a normal body weight is key.[28] Lifetime risk of type 2 diabetes in strata of BMI has previously been quantified in the RS.[17] Among individuals at high genetic risk, those with a normal weight have a substantial lower risk of type 2 diabetes compared to individuals with obesity. This is in agreement with findings from previous reports[13-16] that have provided evidence that preventing obesity through lifestyle intervention attenuates high genetic risk. We add to the current literature quantification of the effect of BMI on the lifetime genetic risk of diabetes.

Our study benefited from evaluating the effect of BMI on genetic risk in two heterogeneous populations. ARIC and RS participants experience culturally distinct environmental influences from diet and physical activity, however, BMI is a cross-cultural risk factor. Furthermore, ARIC had a higher proportion of individuals with obesity, allowing the effect of BMI on genetic risk in individuals with obesity and at high genetic to be evaluated with more precision.

Our study has several limitations. First, the GWAS of type 2 diabetes from which we derived the genetic variants mainly includes individuals of European ancestry. As such we restricted our analysis in the ARIC study and the RS on participants of European ancestry. It is therefore unclear whether our results are generalizable to other ancestral groups.[29] Second, we included individuals aged 45 years and older, and thus estimation of the lifetime risk was not from birth. While individuals who develop type 2 diabetes prior to age 45 may have a stronger genetic component,[30] the vast

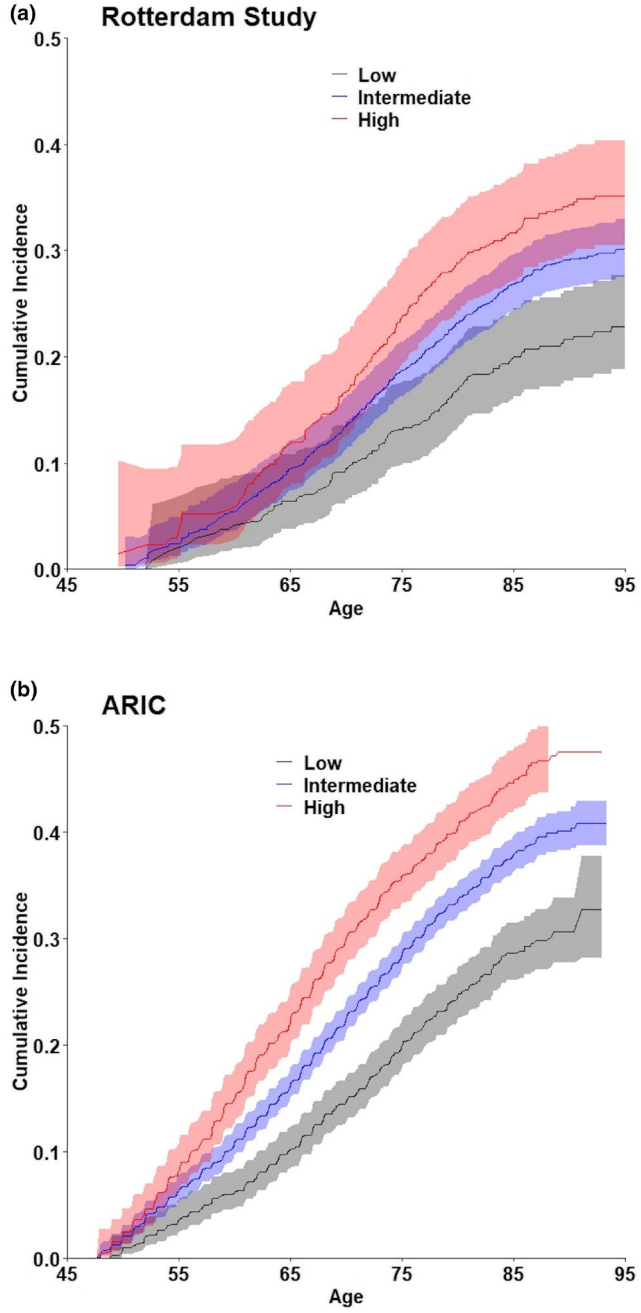

FIGURE 2 Lifetime risk of incident type 2 diabetes in individuals aged 45 years by genetic susceptibility, adjusted for the competing risk of death in the ARIC study (A) and Rotterdam Study (B). Cumulative incidence of type 2 diabetes in individuals aged 45 years stratified by genetic risk, adjusted for the competing risk of death free of diabetes

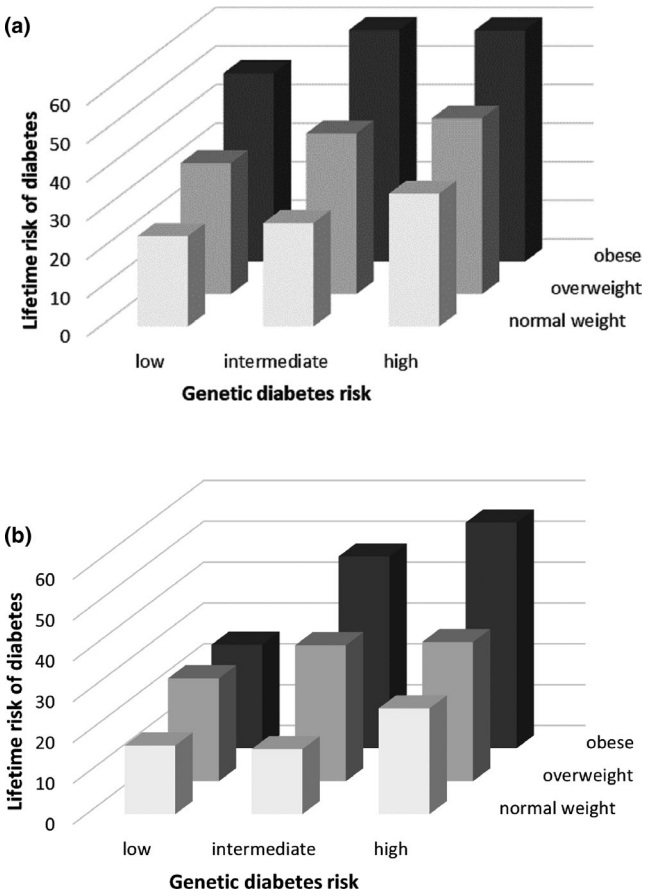

FIGURE 3 Lifetime risk of type 2 diabetes at the age of 45 years for low, intermediate and high genetic risk individuals, stratified by BMI category in the ARIC study (A) and Rotterdam Study (B). The remaining lifetime risk of diabetes in individuals aged 45 years for low, intermediate and high genetic risk, and stratified by BMI category

majority of cases of type 2 diabetes are diagnosed beyond the age of 45.[31] Furthermore, HbA1c was not measured at the study centre visits in both the ARIC and RS which may have resulted in a small number of false negatives with respect to diabetes diagnosis. We constructed a polygenic score based on common genetic variants described in the largest GWAS to date on type 2 diabetes. However, these variants only explain an estimated 18% of the heritability of diabetes.[5] Furthermore, recent whole-exome and whole-genome sequencing studies in isolated populations have identified uncommon and rare variants that constitute a higher relative risk of developing diabetes compared to most common risk variants identified in the GWAS.[32-34] The inclusion of common, uncommon and rare genetic variants in a genetic score for diabetes may further improve its discriminative ability to identify individuals at risk of diabetes. Ongoing studies with access to exome and whole-genome sequence data should provide answers to this pending question. Notably, we used BMI as a measure of obesity. However, due to sarcopenia, BMI may not be an accurate measure of obesity in the elderly that may lead to misclassification. Last, we did not assess the effect of various environmental factors including physical activity and sleep disorders that may modulate the observed effect estimates.

In conclusion, the lifetime risk of type 2 diabetes varies markedly according to genetic susceptibility. In individuals at high genetic risk, maintaining normal weight may mitigate their genetic predisposition, emphasizing the importance of obesity prevention in type 2 diabetes prevention.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest.

AUTHOR CONTRIBUTIONS

S.L. and NRH designed the study, analysed the data and drafted the manuscript. FA, TTWvH, MJGJ, AGU, EJGS, ACM, EB, JSP, ES, MAI and MK provided data interpretation and meaningful contributions to the revision of the manuscript. AD and PSdV supervised the work, provided data interpretation and meaningful contribution to the revision of the manuscript. SL, NRH, PSdV and AD take responsibility for the integrity of the data and accuracy of the data analysis.

DATA AVAILABILITY STATEMENT

Genotype and phenotype data of the ARIC (dbGaP Study Accession: phs000280.v3.p1) are available via dbGaP. Due to restrictions based on privacy regulations and/or informed consent of the participants, data cannot be made freely available in a public repository for the Rotterdam Study. Data of these studies can be obtained upon request. Requests for Rotterdam Study data should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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