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The link between Family History and risk of Type 2 Diabetes is Not Explained by Anthropometric, Lifestyle or Genetic Risk Factors: the EPIC-InterAct Study

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Abstract

Aims/hypothesis—Although family history of type 2 diabetes (T2D) is a strong risk factor for the disease, the factors mediating this excess risk are poorly understood. In the InterAct case-cohort study we investigated the association of family history of diabetes among different family members with incidence of T2D and the extent to which genetic, anthropometric and lifestyle risk factors mediated this association.

Methods—13,869 individuals (including 6,168 incident cases of T2D) had family history data available, and 6,887 individuals had complete data on all mediators. Country-specific Prentice-weighted Cox models were fitted within-country and hazard ratios (HR) combined using random-effects meta-analysis. Lifestyle and anthropometric measurements were performed at baseline and a genetic risk score comprising 35 T2D-associated polymorphisms was created.

Results—A family history was associated with higher incidence of T2D (HR:2.72(95%CI: 2.48-2.99)). Adjustment for established risk factors including BMI and waist-circumference only modestly attenuated this association (HR:2.44(95%CI:2.03,2.95)); the genetic score alone explained only 2% of the family history-associated risk of T2D. Greatest risk of T2D was observed in those with a biparental history of T2D (HR:5.14(95%CI:3.74,7.07)) and those with parental diabetes diagnosis at younger age (<50yrs) (HR:4.69(95%CI:3.35,6.58)) - an effect largely confined to maternal family history.

Conclusions/interpretation—Prominent lifestyle, anthropometric and genetic risk factors explained only a marginal proportion of the family history-associated excess risk, highlighting that family history remains a strong, independent and easily assessed risk factor for T2D. Discovering the factors explaining the association of family history with T2D risk will provide important insight into the aetiology of T2D.

Keywords

family history; type 2 diabetes; genetics

Introduction

A family history of diabetes is associated with a range of metabolic abnormalities (1) and is a strong risk factor for the development of type 2 diabetes (T2D) (2-4). It is likely that this elevated risk of T2D is mediated, in part, by both genetic and shared environmental components amongst family members, but the precise factors accounting for this increase in risk are poorly understood. Anthropometric and lifestyle-related risk factors such as BMI, waist circumference, and physical inactivity are major risk factors for T2D (5-7) andaggregation of such traits amongst families (3;8) may account for a portion of the excess risk attributable to family history. However, adjustment for these factors in a previous study of women left most of the family history-association with T2D risk unexplained (3).

Recently, a number of common genetic variants have been associated with T2D (9), although the addition of genetic risk scores of up to 20 T2D-associated variants improved little on the performance of T2D-prediction models already containing family history (10-12). Although a recent study observed a weak association between the number of parents with diabetes and a genetic risk score (13), to date it remains unknown whether common genetic variation associated with T2D explains any of the family history-associated risk.

We therefore investigated the association of family history of diabetes among different family members and by age of familial diagnosis with risk of T2D in a large prospective case-cohort study of European individuals. We examined the extent to which the increased risk associated with a family history was mediated by anthropometric, lifestyle, and genetic risk factors. We also investigated interactions between these factors and family history on T2D risk to establish if family history acts as an independent risk factor over and above these novel genetic and conventional risk factors.

Methods

Participants and study design

The InterAct study (14) is a large, prospective case-cohort study of 27,779 individuals from 8 European countries nested within the European Prospective Investigation into Cancer and Nutrition (EPIC) (15). The InterAct study, drawn from a total cohort of 340,234 individuals comprising 3.99 million person-years of followup, was designed to investigate the interplay between genetic and lifestyle factors on the risk of T2D. It comprises 12,403 incident T2D cases and a representative subcohort (N=16,154) that also included 778 of the 12,403 incident cases. Family history data were available in 13,869 individuals from 6 countries, including 6,168 incident cases, while 6,887 participants had full availability of mediators and were included in mediation analyses. Written informed consent was obtained from all participants and all study protocols were approved by local Ethics Committees.

Type 2 diabetes case ascertainment and verification

Briefly, and described previously in the InterAct study description paper (14), all InterAct participants were free of known diabetes at baseline. Ascertainment of incident T2D involved a review of existing EPIC datasets using multiple sources of evidence. Incident cases in Denmark and Sweden were identified via local and national diabetes and pharmaceutical registers. For other centres, we sought further verification from no fewer than 2 independent sources, including individual medical records review in some centres. Information from any follow-up visit or external evidence with a date later than the baseline visit was used. Follow-up was censored at the date of diagnosis, 31st of December 2007 or date of death, whichever occurred first. If date of diagnosis could not be ascertained from any of the sources listed above (N=310), the midpoint between recruitment and censoring was used.

Baseline measurements in the EPIC-InterAct study

Briefly, height, weight, waist and hip circumferences were collected at baseline as previously described (16). Physical activity was assessed using a valid brief questionnaire covering occupational and recreational activity levels (17). Smoking status and level of education reached were also ascertained by questionnaire. Adherence to a Mediterranean diet pattern was assessed by food frequency questionnaire as previously described (18), and a blood sample was taken from which DNA could be extracted. Baseline characteristics from centres that ascertained family history are reported both overall and by country in ESM Table 1.

Family history

Family history of diabetes was ascertained by questionnaire at follow-up, unless otherwise indicated, in 6 countries: France, UK, Netherlands, Germany, Sweden and Denmark. Family history data were not available in Italian or Spanish centres, nor in the Oxford or Heidelberg centres, and they were excluded from analyses. In France, participants were asked to report a history of diabetes in their mother and father separately, and the age category (<55, 55-59, 60-64, 65+, unknown age) in which it was diagnosed. At baseline in the UK, information concerning the presence of a family history and age of diagnosis in mother, father or siblings was requested. At baseline in the Netherlands, family history and age of diagnosis in either mother or father was ascertained. At follow up, further information was collected on family history and age of diagnosis for siblings. For the Netherlands and UK, those with familial diabetes diagnosed after the age of 20 were considered to have a positive family history of T2D. For individuals who reported family history information at baseline and at follow-up, we used that from follow-up. In Germany, the presence of diabetes in mother, father, or siblings and the age category at which it was diagnosed (<30 years, 30 to 60, older than 60) were ascertained. Those with family diagnosed after age 30 were considered to have a family history. Similarly, in Denmark the presence or absence of diabetes in mother, father or siblings and whether diagnosed before or after age 35 was collected. Those with familial diagnosis after age 35 were considered to have a family history. In Umeå, Sweden, participants were asked a question on the presence or absence of diabetes in parents or siblings, which allowed us only to establish the presence of diabetes in a first degree relative. Individuals from Umeå were therefore excluded from analyses including categorical family history information. In Malmö, presence of family history was ascertained for mother, father and siblings separately. Availability of family history data by country is shown in ESM Table 2. In centres that ascertained family history, we compared risk factors for T2D among responders and non-responders to the question by linear or logistic regression adjusted for age, sex and centre. This analysis was performed overall (not by country) given the low level of missingness in some countries.

From the above variables, the primary exposure variable: family history in any first-degree relative, was constructed. Where possible, we also classified individuals as having different, non-exclusive degrees of family history: parental, sibling, maternal, paternal or biparental. In countries and centres with data on both parents and siblings separately, a variable was also constructed to count the number of family members reported to have had diabetes.

Genotyping and genetic risk score

Genotyping of 35 SNPs associated with T2D (9;19-22) (ESM Table 3) was undertaken using a Sequenom iPLEX array (Sequenom Inc., California), or by TaqMan (Applied Biosystems). Those homozygous for the risk allele at each locus were dummy-coded as 2, heterozygotes as 1, and those carrying no risk alleles as 0. A genetic risk score was constructed by summing the number of risk alleles. To maximise sample size, missing genotypes were imputed by assigning the mean genotype at each locus for cases and non-cases separately for individuals successfully genotyped for at least 30 of the 35 loci. In total 2,272 individuals had a part of their genetic score imputed, although the vast majority of these individuals (77%) had only one of the 35 SNPs imputed. No genotyping data were available for individuals from Denmark (N=3,068)

Statistical analysis

To estimate the association between family history and incident T2D, Prentice-weighted Cox regression models with age as the underlying timescale were fitted within countries and hazard ratios combined using random effects meta-analysis (23;24). For interactions, effect estimates from the relevant product terms were also meta-analysed as above. Unless otherwise specified all models were adjusted for sex and centre. When number of affected family members was included in a model, we did not stratify by country due to low numbers with more than two affected family members. In analyses comparing the association of family history with T2D by age of familial diagnosis, only UK and Netherlands had information available on actual age of diagnosis. For analyses of the association of family history with T2D by age of participant diagnosis, we compared the association of family history with T2D using cases diagnosed at or before and after the age of 60 years (1,862 and 4,306 cases, respectively).

Comparisons of quantitative characteristics between subcohort participants with and without family history were performed by linear regression, and by logistic regression for binary variables, adjusted for age, sex and centre.

We included BMI, waist and hip circumference, diet, physical activity, smoking status, level of education and a genetic risk score as potential mediators of the family history-associated risk of T2D. In mediation analyses, the sample was restricted to those with full availability for each mediator. In full case-cohort analyses, the proportion of the family history-association mediated was calculated as $(1-(\ln HR_{\text{adjusted model}})/\ln HR_{\text{crude model}})$(25). We performed additional mediation analyses including only individuals in the subcohort by logistic regression as previously described (26). Briefly, this method allowed estimation of the indirect effect of family history (IE) (equal to the product of the family history-mediator and mediator-diabetes coefficients), the direct effect (i.e. that mediated directly by family history, independent of the mediator(s)) and the total effect of family history (TE) (i.e. unadjusted for any potential mediators).

We also investigated the added value of including family history or the genetic score to a basic model containing age, sex and BMI for prediction of diabetes incidence using logistic regression. The effect of adding further variables to the basic model was assessed by

comparison of the respective areas under the curves (AUC)(27). The inclusion of a categorical family history variable (individuals having zero, one, two, or three family members with T2D) was compared to the conventional family history classification of either having none or any family history of the disease. We also investigated the effect of adding either the genetic score or a single question on the presence or absence of family history to the model containing age, sex, and BMI on predictive performance.

Results

Individuals with a family history of diabetes in any first degree family member were at higher hazard of T2D (HR: 2.72 (95% CI: 2.48, 2.99); I^2=15.7, $P_{heterogeneity}$=0.31) (Figure 1, ESM Figure 1). Although the proportion of individuals answering questions on family history and reporting positive family history differed amongst countries (ESM Table 4), between-country heterogeneity in the association of family history with T2D was low for all degrees of family history ($I^2 \leq 20\%$). The presence of diabetes in different family members was associated with a similar hazard ratio of T2D (Figure 1), although having a biparental family history was associated with higher hazard (HR: 5.14 (3.74, 7.07)). Having any one family member with T2D was associated with a 2.5-fold increase in hazard of T2D (HR: 2.56 (2.41, 2.72)), while having 2 (HR: 3.99 (3.58, 4.43)) or 3 family members (HR: 5.73 (4.28, 7.67)) with T2D was associated with even higher risk. We observed no difference in the association between family history and T2D whether ascertained at baseline or follow-up ($P_{heterogeneity}$=0.44). In centres that ascertained family history, individuals with that data missing were younger and more likely to be male. After adjustment for age, sex and centre, non-responders also had higher BMI (Difference in means: 0.53 kg/m^2 (0.32, 0.74)), hip (0.47cm (0.05, 0.88)) and waist circumference (1.54 cm (1.00, 2.09)). But we observed no difference in T2D incidence between responders and non-responders after BMI adjustment (HR: 1.04 (0.98, 1.11); P=0.23).

Parental diagnosis at or before age 50 was associated with a higher hazard of T2D (HR: 4.69 (3.35, 6.58)) than parental diagnosis after age 50 (HR: 2.61 (2.17, 3.14)) ($P_{heterogeneity}$=0.003) (Figure 1). This effect was largely confined to maternal family history: maternal diabetes diagnosed at or before the age of 50 (median age of diagnosis: 45 years) was associated with a higher hazard (HR: 6.00 (3.94, 9.12)) than maternal diagnosis after age 50 (HR: 2.67 (2.16, 3.30)) ($P_{heterogeneity}$=0.001). We observed some suggestion that family history had a greater association with diabetes risk in InterAct participants diagnosed before 60 years old ((HR: 3.14 (2.57, 3.84)) than those diagnosed after age 60 ((HR: 2.53 (2.28, 2.80)) (($P_{heterogeneity}$=0.058).

After adjustment for age, sex and centre, those with family history of T2D had higher BMI, hip and waist circumferences, and had reached lower levels of education, and had a higher genetic risk score (Table 1). The genetic score was strongly associated with T2D incidence (β per-allele=1.08 (1.06, 1.10), $P=1.5\times10^{-17}$). These risk factors for T2D were subsequently considered as potential mediators of the family history-associated risk. Restricting analyses to those with full availability of the above risk factors had little effect on the risk associated with family history (Figure 2). Adjustment for waist circumference had the largest effect of any single risk factor, but explained only 11% of the family history association with T2D

risk. Furthermore, adjustment for BMI, waist and hip circumference, smoking, diet, physical activity, education level and genetic risk score together explained only 13% of the risk of T2D associated with family history (Figure 2). In subcohort analyses where we estimated the indirect effect of family history via each mediator, only BMI, waist and hip circumference accounted for a statistically significant portion of the family history association (Table 2). A larger proportion of the maternal family history association with T2D is explained by these risk factors than for paternal family history (17% Vs. <1%) (Figure 2, ESM Table 5). Although mean genetic score was higher in individuals with family history (P=0.002) (Table 1), the genetic score alone explained only 2% of the family history association (Figure 2, Table 2), and a similarly small proportion for all degrees of family history (ESM Table 5). Despite being established prominent risk factor for T2D, physical activity levels were not associated with family history (Table 1), and as such, explained less than 1% of the family history-associated T2D risk (Figure 2, Table 2).

A nominally significant interaction was observed between family history and physical activity (P=0.048), although inactivity was associated with higher T2D incidence, regardless of family history (ESM Table 6). Given the absence of interaction, family history in combination with PA, genetic risk score, and particularly BMI, identified individuals at high risk of T2D (ESM Table 6). For example, obese individuals with a family history had a 22-fold increased T2D incidence relative to those with no family history and normal BMI.

Including information on the number of family members with T2D and comparing to a model containing only a yes/no classification of family history, we observed only a very marginal increase in AUC (0.791 Vs 0.790, P=0.039). Inclusion of the genetic risk score in the model resulted, again, in a very marginal increase in AUC (0.818 Vs 0.809, $P < 0.001$) compared to a model including age, sex, centre, BMI and family history. In addition, in comparisons between adding either a single question on family history information or the genetic risk score to a prediction model (containing age, sex, and BMI), the single question resulted in larger improvement in AUC (0.810 Vs. 0.792, $P < 0.001$) than the genetic risk score (AUC: 0.803 Vs. 0.792, $P < 0.001$).

Discussion

Family history was associated with T2D incidence with no evidence of heterogeneity between European countries. Individuals with more than one relative with diabetes or with younger maternal diagnosis had even higher risk. The majority of the risk associated with family history was unexplained by major risk factors including BMI and physical inactivity. Although individuals with a positive family history had a mean BMI of almost 1kg/m^2 higher than those without (Table 1), variation in BMI explained less than 9% of the family history association with T2D risk, less than the 21.1% found in a previous study in women only (3). Our observation that maternal and paternal family history-associated risks were explained to different extents by established risk factors also hints at a different aetiology of the family history-associated risk in different family members. Overall, adjustment for multiple anthropometric, lifestyle and genetic risk factors explained only 13% of the family history-associated T2D risk (Figure 2), the genetic risk score alone explaining only 2%.

Heritable lifestyle behaviours and anthropometric characteristics such as physical activity (28) and BMI (29) are strong risk factors for T2D (5;6) and good candidates to mediate the family history-associated risk of diabetes. Admittedly, the precision of measurement of physical activity is limited by the large scale of the EPIC project, but even for more easily measured risk factors such as BMI, they mediate a small proportion of the association (Figure 2, Table 2). While the important role of shared environmental factors is supported by findings that diabetes in a spouse is associated with increased risk (30), the only other study to investigate mediation of family history-associated risk in a large prospective setting also found that major lifestyle and anthropometric risk factors explained only a minority of the associated risk in women (3). Previous studies of adoptees found that they had no increased risk of T2D from family history of diabetes in their adoptive parents, but a sustained increase in risk when their biological parents had diabetes (31), supporting the notion that genetic and/or intrauterine influences may mediate a significant proportion of the family history association. However, the genetic risk score comprising 35 variants associated with T2D explained only 2% the family history-association with T2D risk (Table 1). Admittedly, these common variants explain little of the overall variation in T2D risk (9), which may explain the small proportion of the family history association they appear to mediate. It is likely that presently unknown genetic variation, gene-environment and epistatic interactions account for a proportion of this association. Although practical and computational limitations have constrained large-scale investigation of such effects to date, overlooking them may contribute to the inability to explain complex traits with apparently large familial components (32). Ongoing sequence-based efforts to identify rare and low frequency T2D-risk alleles should help to clarify this question.

Parental diabetes diagnosed at younger age was associated with a higher risk of T2D (Figure 1): an effect largely confined to those with younger maternal diagnosis of T2D. In mothers diagnosed before the age of 50, the median age of diagnosis was 45 years of age, which suggests that a minority of mothers had overt diabetes during pregnancy, but may indicate the presence of perinatal dysglycaemia. A family history of diabetes is associated with metabolic abnormalities (1), the extent of which was found to be greater in those with a family history diagnosed at younger age (33). It has also been reported that individuals with young maternal diagnosis of T2D had a greatly increased odds of impaired glucose tolerance (2); an effect not observed for younger paternal diagnosis. Furthermore, studies in high risk populations suggest that maternal dysglycaemia during pregnancy even below the diabetic or impaired glucose tolerance thresholds is associated with higher T2D risk in offspring (34). An accumulating body of evidence from animal models also supports the existence of epigenetic effects conferred by the intrauterine environment on disease risk, (35;36). These findings also suggest that not only information on the extent of family history (i.e. how many family members), but also the nature of family history and age of diagnosis, particularly maternal diagnosis, may provide further insight into individual T2D risk. We noted that the extent to which maternal and paternal family history-associated risk of diabetes is explained by our proposed mediators differs. Overall, we observe that 17% of the maternal and less than one percent of the paternal family history associated-risk is explained by the same mediators (ESM Table 5). This finding suggests that the T2D risk attributable to family history may have distinct aetiology depending on the family member affected, and is

supported by observations of distinct metabolic perturbations dependent on the affected parent (1).

Inclusion of categorical information on the extent of family history marginally improved prediction relative to a yes/no classification of family history. Although addition of the 35 SNP genetic risk score also marginally improved prediction, extra family history information is more easily ascertained in the clinical setting and we noted that even a single question on the presence of familial T2D performed better than the genetic risk score in predicting T2D. Despite previous suggestions of potential interactions of family history with lifestyle factors (8;37) the evidence for interactions in our study was weak (ESM Table 6). In groups already at high risk of diabetes by virtue of obesity or physical inactivity, family history is still associated with even higher risk: obese individuals with a family history were at more than 20-fold higher risk compared to lean individuals without family history (ESM Table 6). Importantly, however, lower BMI and higher levels of physical activity were associated with a lower risk of T2D, regardless of family history. Despite fatalistic perceptions among some with a family history of T2D (38), individuals with family history are likely to adopt “healthy” behaviours when advised to do so by a physician (39). Our findings suggest that individuals with a family history of diabetes have much to gain from such lifestyle intervention.

Strengths and limitations

We have used a large sample of verified incident T2D cases nested within a very large multinational cohort study with standardised assessments of exposure and outcomes. The diversity of the cohort in terms of lifestyle, anthropometric and social characteristics allows a robust assessment of the mediation of family history by these factors. Given the absence of DNA in some participants and incomplete availability of other mediating variables, the sample size in the mediation analyses is smaller than in overall analyses. However, we observe near-identical associations between family history and diabetes in both the overall and restricted sample, and therefore believe that the reduced sample size has minimal impact on the generalizability of our mediation estimates. While ascertainment methods of cases in InterAct were heterogeneous across countries, again, we observe little heterogeneity in associations between countries. InterAct cases in the study were clinically diagnosed, and it is possible that those reporting a family history have increased frequency of testing for diabetes, which may serve to strengthen the observed association. However, we observe no interaction between prominent risk factors such as BMI and family history on risk of T2D (one may expect an even higher frequency of testing when these risk factors are present in combination). Family history information was not always available at baseline but we found no heterogeneity in the association between family history and hazard of T2D whether ascertained at baseline or at follow up. Although we tried to be specific to family history of T2D, it is possible that we may have included people who truly had a family history of type 1 or other forms of diabetes. However, the potential level of misclassification is low, given the lower prevalence of type 1 diabetes. Also, the direction of any bias in our estimate of the association between family history of diabetes and incident diabetes would be to underestimate the true association if familial type 1 diabetes is not associated with type 2 diabetes risk. However, familial type 1 diabetes has also been suggested to be associated

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with risk of T2D (40), in which case, any misclassification would have little impact on our estimates. For analyses of multiple family history of diabetes or sibling family history, no information was available on family size.

Conclusions

We found that even after accounting for prominent T2D risk factors such as physical activity, BMI, waist circumference and a multi-SNP genetic risk score, family history was strongly associated with future risk of T2D, and that the majority of this risk remained unexplained. The independence of family history as a risk factor, and relative ease with which it can be ascertained means that establishing family history of disease remains of primary clinical importance in this genomic era: a single family history question outweighed the added predictive power of the genetic risk score. Furthermore, given the modest mediation of family history-associated risk of diabetes by major risk factors, genetic and otherwise, greater insight into how family history contributes to risk of type 2 diabetes would represent an important advance in our understanding of the aetiology of the disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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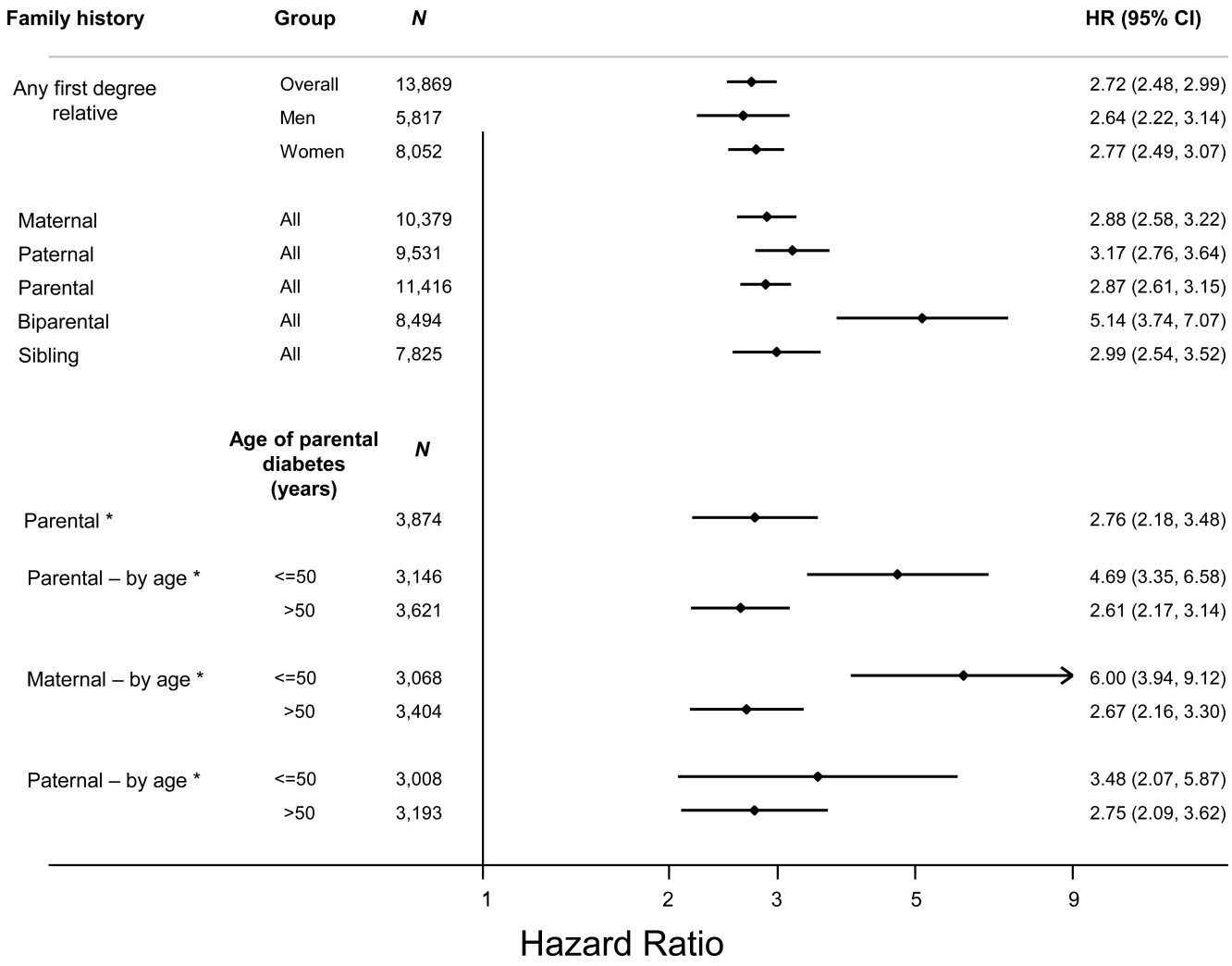

Figure 1. Association of degrees of family history with risk of T2D in men, women and overall: The EPIC-InterAct study

Referent groups were individuals with no reported family history of diabetes.

*Only UK and Netherlands had sufficient data available on age of diagnosis of parental diabetes and these analyses are restricted to those two countries.

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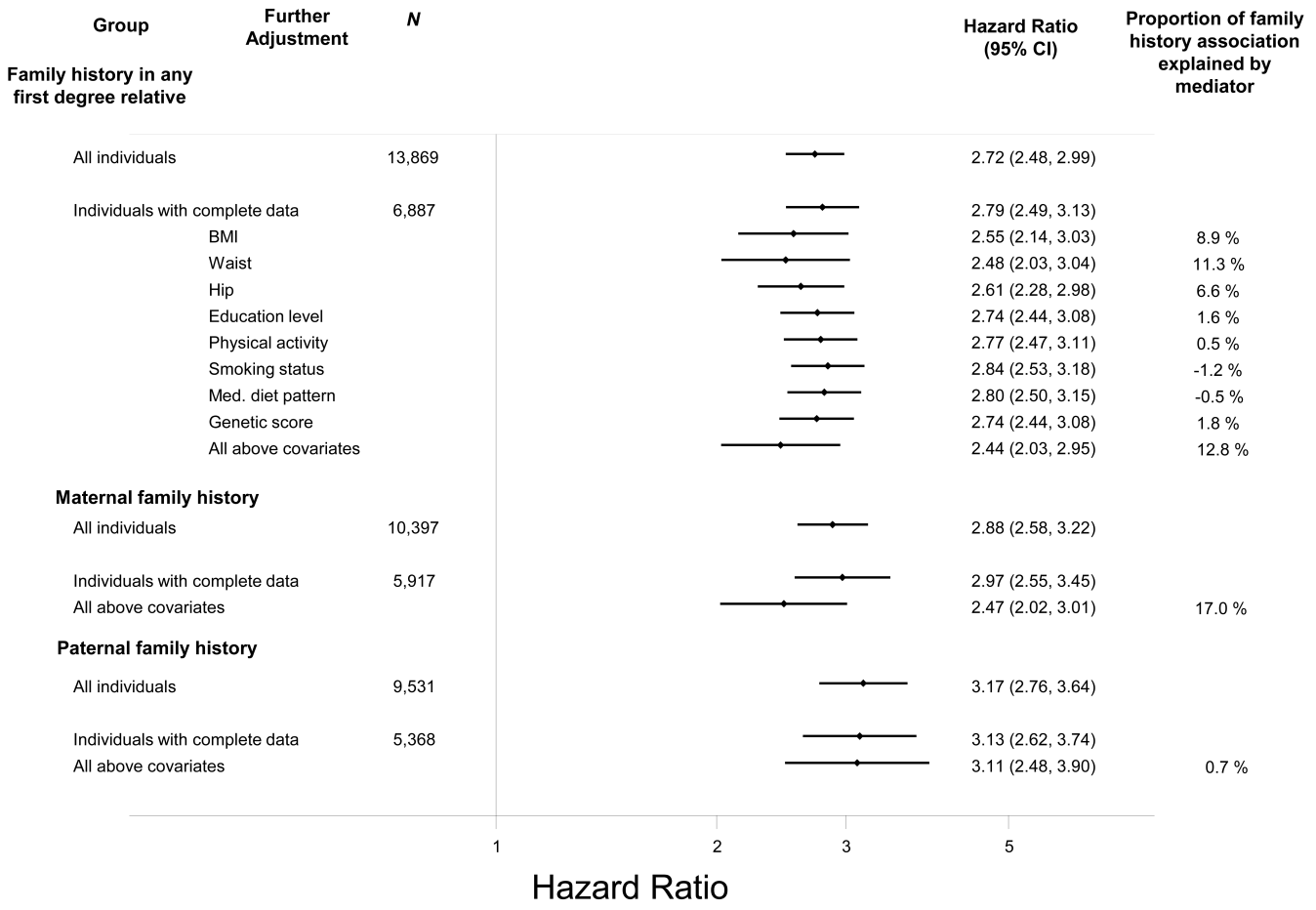

Figure 2. Association of family history with T2D risk after adjustment for potential mediators in individuals with full availability of mediators

All analyses were adjusted for sex and centre. Models were then individually adjusted for each specified risk factor, and all mediators where specified. The proportion of the family-history effect explained by each mediator was calculated as $(1-(\ln HR_{\text{adjusted model}}/\ln HR_{\text{crude model}})$

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Table 1

Baseline characteristics by family history status in the subcohort: The EPIC-InterAct study

	No family history			Positive family history			Age-, sex- and centre-adjusted difference in means		
Characteristic	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**Difference**	**95% CI**	***P***
Age at recruitment (years)[a]	6541	54.0	9.7	1503	54.0	9.0	0.27	(−0.19, 0.73)	0.25
Sex (% Men)[b]	6541	2512 (38%)		1503	462 (31%)		1.33	(1.17, 1.52)	<0.001
BMI (kg/m^2)	6528	25.1	3.9	1501	26.0	4.1	0.89	(0.68, 1.11)	<0.001
Height (cm)	6530	168.4	9.0	1501	167.5	8.7	−0.10	(−0.45, 0.25)	0.57
Weight (kg)	6531	71.5	13.6	1501	73.2	13.9	2.45	(1.80, 3.10)	<0.001
Weight at age 20 (kg)	3704	62.4	10.3	835	62.5	10.3	1.00	(0.40, 1.60)	0.001
Waist circumference (cm)	5685	84.1	12.4	1342	85.6	12.4	2.39	(1.8 , 2.99)	<0.001
Hip circumference (cm)	5682	99.9	7.9	1343	101.6	8.5	1.55	(1.08, 2.02)	<0.001
Physical activity index	6390	2.6	1.1	1473	2.5	1.0	−0.05	(−0.11, 0)	0.06
Smoking – Never[b]		2897 (45%)			707 (47%)				
Smoking – Former	6425	1961 (31%)		1490	424 (28%)		0.91	(0.81, 1.02)	0.26
Smoking – Current		1567 (24%)			359 (24%)				
Education level	6414	2.4	1.1	1484	2.3	1.1	−0.12	(−0.18, −0.06)	<0.001
Mediterranean diet pattern (1-3)	6415	1.7	0.7	1467	1.7	0.6	−0.01	(−0.05, 0.02)	0.53
Energy intake (kcal/day)	6415	2105.9	601.5	1467	2031.5	579.1	−29.85	(−60.0, 0.33)	0.05
Genetic score	3387	36.7	3.7	841	37.1	3.8	0.37	(0.09, 0.65)	0.01
Genetic score (including imputed genotypes)	4362	36.8	3.7	1083	37.2	3.7	0.39	(0.15, 0.64)	0.002

Individuals with no family history are the reference group throughout. Analyses include all individuals in centres that collected information on family history and had data on each individual characteristic available.

[a] Adjusted for sex and centre only

[b] Difference assessed by logistic regression adjusted for centre (Men=0, Women=1; Never smokers=0, ever smokers=1) and odds ratio reported.

Physical Activity index and Education level were treated as continuous variables for the purpose of this analysis (Physical activity index (1=inactive, 2=moderately inactive, 3=moderately active, 4=active; Education level: 0=none, 1=primary school, 2=technical school, 3=secondary school, 4=degree or higher education)

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Table 2

Mediation analyses in the InterAct subcohort participants with full availability of mediators

	Subcohort only[a] (N=4,154; 154 Cases)			
Mediator	**Total Effect (TE)**	**Direct Effect (DE)**	**Indirect effect (IE)**	**Proportion Mediated (%) ((ln(IE)/ln(TE))**
BMI	2.92 (2.02, 4.11)	2.72 (1.9, 3.88)	1.15 (1.08, 1.22)	12.7 (6.8, 18.6)
Waist Circumference	2.92 (2.02, 4.11)	2.65 (1.85, 3.8)	1.17 (1.09, 1.26)	14.9 (8.4, 21.3)
Hip circumference	2.92 (2.02, 4.11)	2.77 (1.95, 3.93)	1.11 (1.05, 1.17)	9.7 (4.8, 14.6)
Education Level	2.92 (2.02, 4.11)	2.89 (2.05, 4.07)	1.02 (1, 1.04)	1.8 (−0.2, 3.9)
Genetic risk score	2.92 (2.02, 4.11)	2.88 (2.04, 4.06)	1.02 (1, 1.04)	1.9 (−0.2, 4)
Physical activity index	2.92 (2.02, 4.11)	2.93 (2.08, 4.13)	1 (0.99, 1.01)	−0.2 (−1.2, 0.6)
Mediterranean diet pattern	2.92 (2.02, 4.11)	2.92 (2.07, 4.12)	1 (1, 1)	0 (−0.1, 0.1)
Smoking	2.92 (2.02, 4.11)	2.95 (2.09, 4.16)	0.99 (0.97, 1.01)	−0.1 (−2.5, 0.5)
All of the above	2.92 (2.02, 4.11)	2.65 (1.84, 3.81)	1.19	16.16

TE shows the association between family history and incident diabetes unadjusted for any mediators. DE is the direct effect of family history independent of the specified mediators, while IE is the indirect effect of family history via the specified mediator.

[a] Analyses were performed in the subcohort only using logistic regression to model the log odds of being a case, adjusted for age, sex and centre of recruitment and restricted to individuals with full availability of mediators