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ARTICLE

The impact of family history of diabetes and lifestyle factors on abnormal glucose regulation in middle-aged Swedish men and women

A. Hilding · A.-K. Eriksson · E. E. Agardh · V. Grill · A. Ahlbom · S. Efendic · C.-G. Östenson

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Abstract
Aims/hypothesis We investigated associations between abnormal glucose regulation and family history of diabetes, separately and in combination with lifestyle risk factors.
Subjects and methods This cross-sectional study comprised 3,128 men and 4,821 women, aged 35–56 years, half with a family history of diabetes. Oral glucose tolerance testing identified subjects with previously undiagnosed prediabetes (IFG, IGT) and type 2 diabetes. Information on lifestyle factors was obtained by questionnaire. Biological interaction was measured with the synergy index.
Results A family history of diabetes conferred a higher odds ratio (OR) for type 2 diabetes in men (OR=3.1, 95% CI 1.7–5.6) than in women (OR=1.7, 95% CI 1.0–3.0), and the synergy index was 2.8 (95% CI 0.9–9.0), suggesting interaction between a family history of diabetes and sex. For prediabetes and diabetes combined, the synergy index was 1.7 (1.0–2.8). Exposure to only one lifestyle risk factor (obesity, physical inactivity, smoking or low sense of coherence [a psychosocial index]) increased the risk to a similar extent in men and women. Combined exposure to a family history of diabetes and lifestyle-related risk factors had a greater effect on type 2 diabetes than any of these factors alone, especially in men. However, analysis of interaction between a family history of diabetes and the lifestyle factors did not indicate any interaction for diabetes, but did indicate interaction for a family history of diabetes and obesity in women with prediabetes.
Conclusions/interpretation Our data suggest a more pronounced effect of a family history of diabetes on the risk of type 2 diabetes in men than in women. While both a family history of diabetes and lifestyle risk factors had effects on type 2 diabetes, irrespective of sex, these effects did not appear to interact.

Keywords Abnormal glucose regulation · Biological interaction · Family history of diabetes · Lifestyle risk factors · Type 2 diabetes

Abbreviations

CGI	combined glucose intolerance
FHD	family history of diabetes
OR	odds ratio
SI	synergy index
SOC	sense of coherence
WHO	World Health Organization

A. Hilding (✉) · A.-K. Eriksson · E. E. Agardh · V. Grill · S. Efendic · C.-G. Östenson
Department of Molecular Medicine and Surgery, Endocrine and Diabetes Unit, Karolinska Institute, Stockholm, Sweden
e-mail: agneta.hilding@ki.se

A. Ahlbom
Stockholm Centre for Public Health and Department of Epidemiology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden

Introduction

It is amply documented that the risk of developing type 2 diabetes is increased by factors related to lifestyle [1–4]. In addition, genetic predisposition plays a major role in the pathogenesis of the disease [5, 6]. The nature of the contributing genes is still unclear. We have limited knowledge about differences between sexes in the impact

of environmental factors and heredity and the combination of lifestyle and heredity on the risk of diabetes.

We recently reported that a family history of diabetes (FHD) and male sex are associated with increased prevalence of type 2 diabetes and milder forms of glucose abnormalities [7]. The aim of the present study was to further explore the influence of FHD on type 2 diabetes, separately for men and women, and with particular focus on combinations of FHD and lifestyle-related risk factors, such as obesity, physical inactivity, smoking and a low sense of coherence (SOC), which were tested for biological interaction. The sex issue is of particular interest, since evidence of a change from female to male preponderance regarding type 2 diabetes in middle age has been observed during recent decades [8].

Subjects and methods

Study population

The present study was part of the baseline epidemiological survey of the Stockholm Diabetes Prevention Programme. The design of this population-based cross-sectional study has been described elsewhere [4, 9]. Briefly, it comprised men and women, aged 35–56 years and living in the outskirts of Stockholm. To examine the impact of heredity of diabetes, the sample was enriched by two sequential procedures (Fig. 1).

A short questionnaire was sent to all men and women of appropriate age, asking about their country of birth and the presence of diabetes in the subject and in relatives. Answers were obtained from 79% (10,236/12,952) of the men and 85% (16,481/19,416) of the women. Subjects with already known diabetes (2.5% of the men, 1.5% of the women) or of foreign origin (2.1% of the men, 7.6% of the women), subjects who had moved or were deceased (0% of the men, 2.0% of the women), and subjects with an unclear (27.4% of the men, 28.5% of the women) or insufficient FHD (15.0% of the men, 9.9% of the women) were excluded at this stage, in total 4,801 men and 8,178 women. Among the remaining respondents we found 2,106 men and 3,583 women with FHD, defined as known diabetes in at least one first-degree relative (mother, father, sister or brother) or at least two second-degree relatives (grandparents, uncle or aunt) and with onset of diabetes at age predominantly above 35 years (fewer than 6% were below 35 years). Furthermore, 3,329 men and 4,296 women were identified as having no known diabetes in their family, i.e. they did not have first- or second-degree relatives or cousins with known diabetes. Previous gestational diabetes was found in 424 women. From the three female groups, 35- to 44-year-old subjects born in the last third of each month were excluded because of financial restrictions.

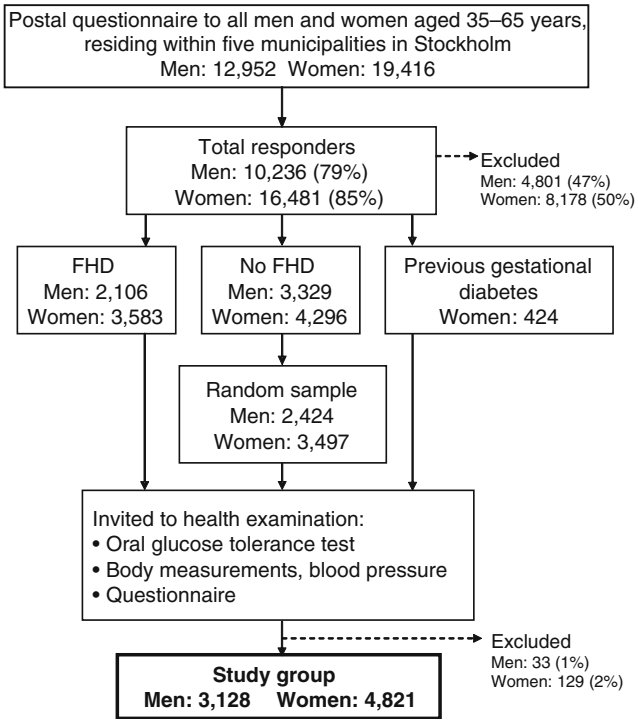

Fig. 1 Study design. Baseline study of men and women in the Stockholm Diabetes Prevention Programme

All subjects with FHD (2,106 men and 3,146 women) along with subjects randomly selected among those without FHD, matched to the first group by age and municipality (2,424 men and 3,497 women), were then invited for examination at a primary health-care centre. Women with gestational diabetes were also invited (n=395). In total, 3,162 (69.8%) men and 4,946 (70.3%) women accepted the invitation. During the examination, the information obtained from the postal questionnaire regarding family background of diabetes was confirmed by questioning the participant. Uncertain heredity and (for women) pregnancy, breast-feeding and medical reasons excluded 33 men and 129 women at this stage. One man did not complete the OGTT and four women had mistakenly been excluded at some earlier point. Thus, the final study group comprised 7,949 individuals (3,128 men and 4,821 women, including 192 with previous gestational diabetes).

Data regarding the men have been reported in part earlier [10]. However, at that time the 1985 World Health Organization (WHO) criteria for classification of glucose tolerance was used [11]. All subjects gave informed consent and the study was approved by the ethics committee of Karolinska University Hospital.

Classification of glucose tolerance

During the health examination a standard 75 g OGTT was performed in the morning after an overnight fast.

Blood was sampled before and 2 h after glucose ingestion. Abnormal glucose regulation was defined according to the WHO 1998 criteria [12]. IFG, IGT, combined glucose intolerance (CGI; IFG+IGT) and type 2 diabetes were defined in relation to NGT. IFG, IGT and CGI were combined in the study and are referred to as 'prediabetes'.

Classification of exposure

During the visit to the health-care centre, the participants confirmed their FHD and answered an extensive questionnaire covering information on lifestyle factors such as physical activity, dietary habits, tobacco use and alcohol consumption, as well as health status and psychosocial conditions.

Measurements of weight and height were performed with the subjects wearing light indoor clothes and no shoes. BMI was calculated; in interaction analyses it was categorised in two ways: <25.0 vs ≥25.0, i.e. normal weight vs overweight (including obesity); and <30.0 vs ≥30.0, i.e. non-obesity vs obesity.

Physical activity was assessed with the question 'How physically active have you been during your leisure time during the last year?', with four response options: (1) sedentary; (2) moderately active; (3) regular exercise; and (4) regular exercise and training [9]. In the interaction analysis, physical activity was categorised into physically inactive (response option 1) and physically active (response options 2–4).

Smoking status was based on questions on current and former consumption in the questionnaire, and subjects were classified as current users or non-current users (including never and former users).

The psychosocial factor measured, SOC, is a paradigm about successful coping with stressors, developed by Antonovsky [13]. The original questionnaire is based on 29 items on the three dimensions of comprehensibility, meaningfulness and manageability [13]. Our analysis of SOC was based on three questions, a simplified method of measurement that is suggested to capture the essence of the three dimensions [14]. A summed index was created from the three alternative responses; according to the distribution of responses among all respondents, SOC was categorised as low (low) and high (lower middle, upper middle, high). Low SOC has been shown to be associated with the risk of type 2 diabetes [4].

Assays

Levels of plasma glucose were analysed in duplicate by a glucose oxidase method using a Yellow Springs Glucose Analyzer (Yellow Springs, Yellow Springs, OH, USA).

Data analysis

Multiple logistic regression was performed to calculate prevalence odds ratios (OR) and 95% confidence intervals of newly detected abnormal glucose regulation. Testing for potential confounders, i.e. BMI (<25.0, ≥25.0 and <30.0, ≥30.0), physical inactivity (sedentary, moderately active and taking regular exercise) and current smoking (yes/no), was done by including them one by one in the logistic regression model. They were retained in the final model if they contributed at least a 10% change in the age-adjusted crude estimate (age in three categories: 35–42, 43–50 and 51–56 years). Biological interaction between two risk factors was evaluated from the adjusted ORs, and analysed by testing whether the joint effect was greater than the sum of the independent effects of the single factors, i.e. departure from additivity [15, 16], by calculating the synergy index (SI) [17]. The SI is defined as equal to $[OR_{11}-OR_{00}]/[(OR_{01}-OR_{00})+(OR_{10}-OR_{00})]$, where the first index digit indicates the absence or presence of FHD and the second index digit indicates the other risk factor. Subjects not exposed to FHD and the other risk factor served as the reference group: $(OR_{00})=1$. Confidence intervals (95%) for the SI were calculated according to the method of Hosmer and Lemeshow [18]. Comparison of continuous variables and categorical variables between two independent groups was assessed by with the unpaired *t*-test and the χ^2 test, respectively. Analyses were conducted separately for prediabetes and diabetes, and for the combined group, in order to increase numbers. Statistical analyses were performed using SAS, version 8.2 (SAS Institute, Cary, NC, USA).

Results

Glucose tolerance and general characteristics in subjects with and without family history of diabetes

According to the 1998 WHO criteria [12], previously undiagnosed abnormal glucose regulation was found in 293 (9.4%) of the men and 271 (5.6%) of the women (Table 1); the prevalences of type 2 diabetes, IFG, IGT and CGI (the last three groups were combined in the analyses and are referred to as prediabetes) being 1.5–2.7 times higher in men than in women.

Frequencies of overweight (BMI ≥25) and obesity (BMI ≥30) were higher in both men and women with FHD compared with those without FHD. Also, the frequencies of physical inactivity and smoking, but not low SOC, were significantly higher in subjects with FHD (Table 2).

Table 1 Distribution of glucose tolerance and family history of diabetes in men and women

	Men (*n*=3,128)	Women (*n*=4,821)
NGT, *n* (%)	2,835 (90.6)	4,550 (94.4)
IFG, *n* (%)	59 (1.9)	48 (1.0)
IGT, *n* (%)	143 (4.6)	145 (3.0)
CGI (IFG+IGT), *n* (%)	26 (0.8)	15 (0.3)
Type 2 diabetes, *n* (%)	65 (2.1)	63 (1.3)
FHD, *n* (%)	1,621 (51.8)	2,583 (53.5)

Abnormal glucose regulation in relation to family history of diabetes and sex

In both men and women, FHD was associated with an increased risk of having abnormal glucose regulation (Table 3). The ORs for prediabetes were similar for both sexes, whereas for type 2 diabetes the OR was higher in men than in women: 3.1 (1.7–5.6) and 1.7 (1.0–3.0), respectively. To assess whether the impact of FHD on abnormal glucose regulation was different in men and women, we conducted an analysis of interaction between FHD and sex (Table 3). Using women without FHD as the reference group, the OR for men without FHD was greater among subjects with prediabetes or type 2 diabetes and in the combined group of prediabetes plus type 2 diabetes. The OR for men with FHD was 2.9 (2.1–3.9) for prediabetes, 4.1 (2.3–7.1) for type 2 diabetes and 3.1 (2.4–4.1) for the combined group, which exceeds the ORs that would be expected had the effects of sex and FHD been independent. This is suggested by the SI, which was 1.4 (0.9–2.4) for prediabetes, 2.8 (0.9–9.0) for type 2 diabetes and 1.7 (1.0–2.8) for the combined group.

Abnormal glucose regulation in relation to family history of diabetes in combination with other risk factors

To evaluate the associations between diabetes heredity and the lifestyle risk factors overweight/obesity, physical inactivity, smoking and low SOC, we studied these factors one by one in combination with FHD and performed interaction analysis (Tables 4 and 5). Thus, subjects were categorised into four groups: (1) subjects not exposed to both FHD and the lifestyle risk factor (serving as the reference group); (2) subjects not exposed to FHD but exposed to the lifestyle risk factor; (3) subjects exposed to FHD but not exposed to the lifestyle risk factor; and (4) subjects exposed to both FHD and the lifestyle risk factor.

Obesity For BMI, the cut-off point of 30.0 (obesity), but not the cut-off point of 25.0, gave sufficient numbers of subjects in all four categories for reliable analysis. In both men and women, obesity without FHD increased the ORs for prediabetes, type 2 diabetes and the combined group of prediabetes plus type 2 diabetes to higher values than non-obesity with FHD. For the combination of obesity with FHD, the ORs were 6- and 11-fold elevated for prediabetes and type 2 diabetes, respectively, in both sexes. The corresponding SI values in men with abnormal glucose regulation suggested that the OR value for the combined exposure is in agreement with FHD and obesity having independent effects. In women, however, an interaction between obesity and FHD was indicated for prediabetes and when prediabetes and type 2 diabetes were added together, SI being 2.2 (1.0–4.5) and 1.8 (1.0–3.2), respectively, whereas for type 2 diabetes no interaction was observed, SI being 1.2 (0.5–2.8).

Table 2 Characteristics of participants and distribution of risk factors according to family history of diabetes in men and women

	Men			Women		
	With FHD (*n*=1,621)	Without FHD (*n*=1,507)	*p* value	With FHD (*n*=2,583)	Without FHD (*n*=2,238)	*p* value
Age (years)	46.6±4.9	46.7±4.9	n.s.	47.5±4.9	47.2±4.9	n.s.
BMI (kg/m^2)	26.5±3.7	25.7±3.3	<0.001	26.0±4.6	24.8±3.9	<0.001
≥25.0	62.7 (1,013)	55.5 (834)	<0.001	52.1 (1,341)	41.0 (916)	<0.001
≥30.0	14.7 (237)	9.2 (138)	<0.001	15.9 (410)	10.0 (222)	<0.001
Physical activity						
Sedentary	11.7 (190)	9.4 (142)	0.041	12.9 (333)	9.3 (207)	<0.001
Current smoking						
Yes	27.6 (447)	24.4 (367)	0.044	28.5 (737)	24.7 (552)	0.003
Sense of coherence						
Low	16.5 (265)	15.6 (232)	n.s.	21.7 (559)	19.7 (441)	n.s.

Continuous data are expressed as mean±SD and categorical data as % (number); the percentage of subjects takes missing values into account
Unpaired *t*-test or χ^2 test, where appropriate, always within sex
n.s. not significant

Table 3 Odds ratios for prediabetes, type 2 diabetes and the combined group of prediabetes plus type 2 diabetes associated with a family history of diabetes in men and women separately and in combinations of family history and sex

	NGT	Prediabetes[a]				Type 2 diabetes				Prediabetes+type 2 diabetes			
	n	*n*	OR	95% CI	SI (95% CI)	*n*	OR	95% CI	SI (95% CI)	*n*	OR	95% CI	SI (95% CI)
Men													
Without FHD	1,409	80	1.0			14	1.0			94	1.0		
With FHD	1,415	148	1.6	1.2–2.1		51	3.1	1.7–5.6		199	1.8	1.4–2.4	
Women													
Without FHD	2,144	67	1.0			18	1.0			85	1.0		
With FHD	2,388	139	1.5	1.1–2.1		44	1.7	1.0–3.0		183	1.6	1.2–2.0	
Combinations of sex and FHD													
Women without FHD	2,144	67	1.0			18	1.0			85	1.0		
Men without FHD	1,409	80	1.8	1.3–2.5		14	1.4	0.7–2.8		94	1.7	1.2–2.3	
Women with FHD	2,388	139	1.5	1.1–2.0		44	1.7	1.0–3.0		183	1.6	1.2–2.0	
Men with FHD	1,415	148	2.9	2.1–3.9	1.4 (0.9–2.4)	51	4.1	2.3–7.1	2.8 (0.9–9.0)	199	3.1	2.4–4.1	1.7 (1.0–2.8)

Biological interaction was analysed using the synergy index (SI)
All analyses are adjusted for age (35–42, 43–50, 51–56), BMI (<25.0, 25.0–29.9, ≥30.0) and physical activity (sedentary, moderately active, regular exercise)
[a] Prediabetes is IFG+IGT+CGI

Using waist circumference (≥102 cm in men, ≥88 cm in women) as a measure of abdominal obesity gave similar results.

Physical inactivity Physical inactivity during leisure time without FHD increased the risk of having prediabetes and type 2 diabetes in both men and women. Although the OR for the combined exposure of physical inactivity and FHD was increased to 9.5 (4.1–22.1) in men with type 2 diabetes, and was three times higher than in women, no obvious biological interaction was indicated either for type 2 diabetes alone or for the combined group of prediabetes plus type 2 diabetes, SI being 1.6 (0.6–4.4) and 0.7 (0.3–1.6), respectively. Also in women, the SI values indicated that physical inactivity and FHD had independent effects when subjects were exposed to both together.

Smoking Current smoking without FHD gave similar ORs for prediabetes as well as for type 2 diabetes in men and women. For the combination of current smoking with FHD, the OR for type 2 diabetes was increased to 4.4 (2.0–10.0) in men, while in men with prediabetes and in women with prediabetes or type 2 diabetes the OR values were lower and comparable to the OR values for exposure to the separate risk factors. However, SI values showed no obvious departure from additivity, in men as well as in women, either for prediabetes or for type 2 diabetes or for these groups combined.

Sense of coherence In the presence of low SOC without FHD, the ORs for prediabetes and type 2 diabetes were similar in the two sexes. For the combination of low SOC with FHD, an approximately two-fold increase in ORs for prediabetes was found in men as well as in women, and for type 2 diabetes in women, whereas a four-fold increase was found for type 2 diabetes in men. The SI values suggested independent effects of low SOC and FHD when both were present in men and women, and also in the combined group of prediabetes and type 2 diabetes.

Discussion

In this cross-sectional study, differences between middle-aged men and women regarding the impact of FHD are demonstrated. Thus, the estimated increased ORs associated with FHD were similar for prediabetes in the two sexes, whereas the OR for type 2 diabetes was higher in men than in women. Interaction analysis indicated synergism between FHD and sex, i.e. a stronger risk of abnormal glucose regulation in men. The combined exposure to FHD and lifestyle-related risk factors had a greater effect on type 2 diabetes than any of these factors alone, especially in men. However, interaction analysis indicated no obvious synergistic effects between FHD and the lifestyle factors, either in men or in women, except for FHD and obesity in prediabetic women.

Table 4 ORs for prediabetes, type 2 diabetes and the combined group of prediabetes and type 2 diabetes associated with combinations of family history of diabetes and BMI, waist, physical activity during leisure time, smoking or sense of coherence in men

Combinations of FHD and other risk factors[a]	NGT	Prediabetes[h]				Type 2 diabetes				Prediabetes+type 2 diabetes			
	n	*n*	OR	95% CI	SI (95% CI)	*n*	OR	95% CI	SI (95% CI)	*n*	OR	95% CI	SI (95% CI)
BMI <30.0 without FHD	1,301	55	1.0			9	1.0			64	1.0		
BMI ≥30.0 without FHD	108	25	5.3	3.1–8.8		5	6.1	2.0–18.6		30	5.3	3.3–8.6	
BMI <30.0 with FHD	1,241	101	1.9	1.4–2.7		35	3.9	1.9–8.2		136	2.2	1.6–3.0	
BMI ≥30.0 with FHD	174	47	6.0	3.9–9.2	1.0 (0.5–1.8)	16	11.1	4.8–25.7	1.3 (0.5–3.2)	63	6.7	4.6–9.9	1.0 (0.6–1.8)
Waist <102 cm without FHD	1,280	51	1.0			8	1.0			59	1.0		
Waist ≥102 cm without FHD	130	29	5.2	3.2–8.5		6	6.1	2.0–17.9		35	5.3	3.3–8.3	
Waist <102 cm with FHD	1,235	103	2.1	1.5–2.9		31	3.9	1.8–8.4		134	2.3	1.7–3.2	
Waist ≥102 cm with FHD	178	45	5.8	3.8–9.0	0.9 (0.5–1.6)	20	14.2	6.1–33.0	1.7 (0.7–3.9)	65	7.0	4.8–10.4	1.1 (0.7–1.8)
Phys. act.[b] without FHD	1,287	64	1.0			10	1.0			74	1.0		
Phys. inact.[c] without FHD	122	16	2.4	1.3–4.3		4	3.9	1.2–12.6		20	2.5	1.5–4.4	
Phys. act. with FHD	1,257	130	1.8	1.3–2.5		37	3.4	1.7–6.9		167	2.1	1.5–2.8	
Phys. inact. with FHD	158	18	1.9	1.1–3.3	0.4 (0.1–1.3)	14	9.5	4.1–22.1	1.6 (0.6–4.4)	32	2.9	1.8–4.6	0.7 (0.3–1.6)
No smoking[d] without FHD	1,071	56	1.0			9	1.0			65	1.0		
Smoking[e] without FHD	337	24	1.4	0.9–2.4		5	1.6	0.5–5.0		29	1.4	0.9–2.3	
No smoking with FHD	1,028	108	1.8	1.3–2.5		32	3.2	1.5–6.7		140	2.0	1.4–2.7	
Smoking with FHD	386	40	1.8	1.1–2.7	0.6 (0.2–1.7)	19	4.4	2.0–10.0	1.2 (0.5–3.1)	59	2.2	1.5–3.2	0.8 (0.4–1.7)
High SOC[f] without FHD	1,183	63	1.0			10	1.0			73	1.0		
Low SOC[g] without FHD	212	16	1.6	0.9–2.8		4	2.3	0.7–7.6		20	1.6	1.0–2.8	
High SOC with FHD	1,176	118	1.7	1.2–2.3		41	3.5	1.7–7.1		159	1.9	1.4–2.6	
Low SOC with FHD	224	29	2.1	1.3–3.4	1.0 (0.3–2.6)	9	3.9	1.5–9.8	0.8 (0.2–2.4)	38	2.4	1.6–3.7	0.9 (0.4–2.0)

Biological interaction was examined using the synergy index (SI)

[a] All combinations are adjusted for age (35–42, 45–50, 51–56 years); combinations with BMI are also adjusted for physical activity (sedentary, moderately active, regular exercise); combinations with physical activity are also adjusted for BMI (<25.0, 25.0–29.9, ≥30.0); combinations with smoking and SOC are also adjusted for physical activity and BMI

[b] Phys. act.=moderately active or taking regular exercise

[c] Phys. inact.=sedentary

[d] No smoking=not currently smoking

[e] Smoking=currently smoking

[f] High SOC=high, upper middle, lower middle

[g] Low SOC=low

[h] Prediabetes=IFG+IGT+CGI

Table 5 Odds ratios for prediabetes, type 2 diabetes and the combined group of prediabetes and type 2 diabetes associated with combinations of family history of diabetes and BMI, waist, physical activity during leisure time, smoking or sense of coherence in women

Combinations of FHD and other risk factors[a]	NGT	Prediabetes[h]				Type 2 diabetes				Prediabetes+type 2 diabetes			
	n	*n*	OR	95% CI	SI (95% CI)	*n*	OR	95% CI	SI (95% CI)	*n*	OR	95% CI	SI (95% CI)
BMI <30.0 without FHD	1,948	50	1.0			9	1.0			59	1.0		
BMI ≥30.0 without FHD	196	17	3.0	1.7–5.4		9	8.1	3.2–20.9		26	3.8	2.3–6.3	
BMI <30.0 with FHD	2,059	79	1.4	1.0–2.0		23	2.2	1.0–4.8		102	1.5	1.1–2.1	
BMI ≥30.0 with FHD	329	60	6.3	4.2–9.4	2.2 (1.0–4.5)	21	11.0	5.0–24.6	1.2 (0.5–2.8)	81	7.1	4.9–10.1	1.8 (1.0–3.2)
Waist <88 cm without FHD	1,793	38	1.0			6	1.0			44	1.0		
Waist ≥88 cm without FHD	346	29	3.4	2.1–5.6		12	7.4	2.7–20.1		41	4.0	2.5–6.2	
Waist <88 cm with FHD	1,859	54	1.3	0.9–2.0		18	2.7	1.0–6.7		172	1.5	1.0–2.2	
Waist ≥88 cm with FHD	534	86	6.5	4.3–9.6	2.0 (1.1–3.6)	26	10.5	4.3–25.9	1.2 (0.6–2.4)	112	7.0	4.9–10.2	1.7 (1.1–2.7)
Phys. act.[b] without FHD	1,955	55	1.0			13	1.0			68	1.0		
Phys. inact.[c] without FHD	189	12	1.7	0.9–3.3		5	2.8	1.0–8.2		17	1.9	1.1–3.4	
Phys. act. with FHD	2,097	108	1.5	1.1–2.1		34	2.0	1.0–3.8		142	1.6	1.2–2.2	
Phys. inact. with FHD	291	31	2.5	1.6–4.1	1.2 (0.4–3.7)	10	3.1	1.3–7.2	0.7 (0.2–2.9)	41	2.6	1.7–4.0	1.1 (0.5–2.7)
No smoking[d] without FHD	1,616	50	1.0			11	1.0			61	1.0		
Smoking[e] without FHD	526	17	1.0	0.5–1.7		7	1.7	0.7–4.5		24	1.1	0.7–1.8	
No smoking with FHD	1,697	111	1.7	1.2–2.4		30	2.0	1.0–4.1		141	1.8	1.3–2.4	
Smoking with FHD	691	28	1.0	0.6–1.6	*	14	2.0	0.9–4.6	0.6 (0.2–2.3)	42	1.2	0.8–1.8	0.2 (0.02–2.0)
High SOC[f] without FHD	1,725	52	1.0			11	1.0			63	1.0		
Low SOC[g] without FHD	418	15	1.0	0.6–1.9		7	2.1	0.8–5.7		22	1.3	0.8–2.1	
High SOC with FHD	1,877	101	1.4	1.0–2.0		32	2.0	1.0–4.0		133	1.5	1.1–2.1	
Low SOC with FHD	509	38	1.9	1.2–2.9	1.9 (0.3–10.4)	12	2.6	1.1–6.1	0.8 (0.2–2.7)	50	2.0	1.3–3.0	1.3 (0.4–3.7)

Biological interaction was examined using the synergy index (SI)

[a] All combinations were adjusted for age (35–42, 45–50, 51–56 years); combinations with BMI were also adjusted for physical activity (sedentary, moderately, regular exercise); combinations with physical activity were also adjusted for BMI (<25.0, 25.0–29.9, ≥30.0); combinations with smoking and SOC were also adjusted for physical activity and BMI

[b] Phys. act.=moderately active or taking regular exercise

[c] Phys. inact.=sedentary

[d] No smoking=not currently smoking

[e] Smoking=currently smoking

[f] High SOC=high, upper middle, lower middle

[g] Low SOC=low

[h] Prediabetes is IFG+IGT+CGI

*Nominator or denominator=0

Dissimilarity between sexes in the prevalence of type 2 diabetes may be dependent on differences in the influence of and exposure to risk factors and how they interact. Heredity is known to play an important role in the aetiology of type 2 diabetes [1, 5, 19]. In the present study, interaction analysis indicated that the impact of FHD on prediabetes and type 2 diabetes was higher in men than in women, and this was also true when the power of the analysis was increased by combining prediabetes and type 2 diabetes. A similar discrepancy between sexes was also found in a screening study of slightly younger subjects (mean age 38 years), in which FHD was associated with diabetes in men but not in women [20]. Moreover, in a study of Swedish women aged 50–59 years [21] no influence of FHD was observed in any of the hyperglycaemic groups. In contrast, in a study of the incidence of type 2 diabetes in slightly older patients (mean age 61–67 years), FHD was suggested to be an important predictor, especially in women [22].

Obesity (BMI ≥30.0) had the greatest influence on the risk of abnormal glucose regulation in men as well as in women. Moreover, exposure to obesity without FHD was associated more strongly with both prediabetes and type 2 diabetes than exposure to FHD without obesity. However, the combined exposure to both FHD and obesity showed the strongest effect. In men no synergistic effect was observed either in prediabetes or type 2 diabetes separately or when calculated together, while in women a synergistic effect between FHD and obesity was observed in the combined group of prediabetes and type 2 diabetes. However, this effect was due to the interaction found among subjects with prediabetes and not among subjects with type 2 diabetes. Thus, it is possible that the interaction between FHD and obesity varies between sexes as well as through the progression of milder forms of abnormal glucose regulation to manifest diabetes. In a large cohort of 32,662 women aged 40–70 years, a biological interaction was found between FHD and obesity in subjects with self-reported type 2 diabetes [23]. Although calculated in another way, by including a product term in the linear regression analysis, a departure from additivity was also observed for FHD and obesity in relation to fasting plasma glucose [24]. When using BMI as the measure of body fatness, this interaction was found only in women, whereas, in contrast to our study, an interaction was found in women as well as in men when waist circumference was used. Estimating biological interaction is relevant, because by identifying groups in which interaction occurs preventive measures can be made more effective. The elimination of one factor may also reduce the risk of the other [15]. However, the use of incorrect approaches when analysing biological interaction may hamper the interpretation of the results [16].

Like type 2 diabetes, obesity has both genetic and lifestyle-related components [5, 25], and high heritability rates have been reported [5, 26]. Our study cannot separate the effects of genetic and lifestyle-related exposures. Thus, the impact of FHD may also include social heredity due to shared exposures to, for example, diets and patterns of physical activity.

Protective components may contribute to lower frequency of type 2 diabetes and the less obvious influence of diabetes heredity in women compared with men. The fact that a minor proportion of the women were postmenopausal (30%) could be of importance. Whereas oestrogen deficiency results in impaired insulin secretion and decreased insulin sensitivity, and in animal models also an increased risk of diabetes, oestrogen replacement therapy results in improvement in these parameters [27–29]. Furthermore menopausal status was significantly associated with diabetes and IGT [30] and menopause appeared to be an important risk factor for diabetes, related to the accumulation of visceral fat and the development of insulin resistance [31]. In this context, sex-specific differences in iron status may also be of interest. Premenopausal women have lower body iron stores, as reflected by serum ferritin concentrations, which gradually increase after menopause, and then approach male levels [32]. Serum concentrations of ferritin have been shown to be associated with levels of glucose and insulin [33], insulin sensitivity [34] and type 2 diabetes [35].

It is of interest to note that the sex difference in the association with type 2 diabetes could also be explained, at least partly, by genes related to diabetes and/or risk factors of the disease. Thus, we have recently shown that polymorphisms in the insulin-degrading enzyme gene are linked to increased BMI and insulin resistance in men but not in women [36]. Similarly, a Leu7Pro polymorphism in the gene for neuropeptide Y, related to regulation of satiety and body weight, was demonstrated to be associated with IGT and type 2 diabetes in men but not in women [37]. In addition, higher serum adiponectin levels in women than in men [38, 39] may contribute to the sex differences in glucose intolerance, since adiponectin levels have been shown to be inversely related to the risk of development of type 2 diabetes [40]. However, the genetic basis for this sex difference is unclear.

There are some issues that should be noted when interpreting the results. The study sample was selected so that half of the subjects had FHD, compared with fewer than the one-quarter originally found among the respondents after the first short questionnaire. Efforts were made to minimise incorrect recall and to exclude relatives with type 1 diabetes. The accuracy of the FHD information was ascertained by asking the subjects twice, first by questionnaire and then by interview when visiting the health-care centre. In addition, a considerable number of subjects who

were unable to fully account for the presence or absence of diabetes among relatives (27.4 and 26.8% of the responding men and women, respectively) were excluded from the study. However, it cannot be excluded that, among those reporting no relative with type 2 diabetes, subjects with hidden FHD could have been found. This is due to the error of undiagnosed diabetes in relatives, a type of under-reporting that could have weakened the observed associations. On the other hand, it has been suggested that type 2 diabetes diagnosed at a younger age is more familial [41]; thus, selective reporting of participants with relatives with early onset diabetes could have strengthened the associations. Since the familial component does not result exclusively from genetic factors but also reflects environmental exposures that are shared by family members, the enrichment of the study group with subjects having FHD may also have affected the levels of other risk factors. It is not likely, however, that sex differences regarding associations between diabetes heredity, other risk factors and glucose abnormality are dependent on the enrichment of the subject group with individuals with FHD, since the same selection criteria were applied in both sexes.

An important advantage of the present study design was that only subjects with previously undiagnosed type 2 diabetes were included. Thus, the participants were unaware of their disease when answering questions on FHD and lifestyle-related components, which minimises recall bias, with no difference between the cases and the referent group.

Furthermore, this cross-sectional study allows us to assess associations of exposure and disease, but precludes analysis of the natural course of development of glucose abnormalities.

In conclusion, our data indicate that FHD affects the risk of abnormal glucose regulation in both men and women and that the effect appears to be stronger in men. Lifestyle-related risk factors also increased the risk in both sexes. While the risk for those with combined exposures was higher than the risk for those exposed only to FHD or to a lifestyle-related risk factor, especially in men, this risk did not exceed what would be expected if the effects of FHD and lifestyle factors were independent, except for FHD and obesity in women. Whether the difference between men and women is present only within the age group we studied (middle-aged) remains unclear. An ongoing follow-up study will show whether the influence of FHD is delayed in women or whether it is unchanged.

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Duality of interest We declare that we have no conflict of interest.

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