Synergy of BMI and family history on diabetes: the Humboldt Study

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Abstract

Objective: To examine the joint effect of family history and BMI on diabetes.
Design: Cross-sectional study.
Setting: A rural community in Saskatchewan, Canada.
Subjects: The analysis was based on data from 2081 adults, 18–79 years of age, who participated in the Humboldt Study conducted in 2003. Doctor-diagnosed diabetes and family history of diabetes of biological parents and siblings were self-reported. Body weight and height were objectively measured. The interaction of family history and BMI on diabetes was assessed on an additive scale.
Results: The prevalence of diabetes was 7·9 %, and BMI and history of diabetes were two important predictors. The adjusted prevalence ratios were 1·76 (95 % CI 1·37, 2·27) and 2·59 (95 % CI 2·05, 3·31) for those with a BMI of 25·0–29·9 kg/m^2 and of at least 30 kg/m^2, respectively, compared with a BMI of less than 25 kg/m^2, and was 2·41 (95 % CI 2·08, 2·80) for those with a family history of diabetes *v.* those without. The data indicated an additive interaction of family history and BMI on diabetes.
Conclusions: When exposed to both family history and overweight/obesity, individuals would have an increased risk that was greater than the sum of their single effects. Reduction of BMI would also reduce the risk of diabetes associated family history.

Type 2 diabetes has increased rapidly internationally. Type 2 diabetes is a complex disorder, and both genetic and environmental factors play an important role in the disease development. Family history of diabetes increases the risk of type 2 diabetes[1–6]. The more cases of diabetes found in a family, the younger the age of onset of type 2 diabetes[7]. Family history of type 2 diabetes is associated with decreased insulin sensitivity and an impaired balance between insulin sensitivity and insulin secretion[8]. A number of genes have been identified to be associated with type 2 diabetes[9–11].

The prevalence of type 2 diabetes is predicted to increase to epidemic proportions in the coming decades, primarily due to lifestyle changes[12]. A rapid increase in worldwide prevalence of obesity is believed to be a main reason[13]. The increase in diabetes prevalence over recent decades has disproportionately comprised persons with high levels of obesity[14–17].

There is increasing evidence for interactions between obesity and genetic factors in the development of diabetes[18]. Obesity modifies the effects of the Asp905Tyr variant of *PPP1R3A* on risk of type 2 diabetes and insulin sensitivity[19]. Obesity is associated with type 2 diabetes only among individuals with high serum γ-glutamyltransferase (GGT) activity, not in those with low serum GGT[20]. A family history of type 2 diabetes is associated with lower sensitivity to activated protein C in overweight and obese premenopausal women[21]. Family history reflects genetic susceptibility in addition to other factors, e.g. common environmental exposures, and we hypothesise that a family history of diabetes modifies the association between obesity and type 2 diabetes and that overweight/obesity is more strongly associated with type 2 diabetes among those with a family history than those without a family history of the disease.

Methods

We conducted a cross-sectional study in the town of Humboldt, Saskatchewan, in 2003. The target population of the study was all the town residents 6 years of age or

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more and was conducted among children (6–17 years) and adults (18–79 years), separately; the present analysis was based on data from adult residents only. A total of 2090 adult residents, 18–79 years of age (71 % of the target population), participated in the study, and the study methods have been detailed in earlier reports[22,23]. Briefly, canvassers contacted all households within the town and surrounding areas and asked all eligible adult subjects in each home to participate in the study and to complete a written consent of participation. A questionnaire left by the canvassers was completed in the home by each subject and returned during a pre-arranged clinic visit. Written informed consent was obtained from each participant. The present study was approved by the University of Saskatchewan Research Ethics Board.

Respondents who answered the following question affirmatively were considered as having diabetes: 'Has a doctor ever said you had diabetes?' Family history of diabetes was obtained by asking questions if their biological parents/sibling had diabetes. Weight was measured to the nearest 0·1 kg using a calibrated hospital spring scale with subjects dressed in normal indoor clothing without shoes. Height in centimetres was measured against a wall using a fixed tape measure with participants standing shoeless on a hard surface. BMI was calculated as weight (kg)/height^2 (m^2). Subjects were grouped into three categories based on BMI (<25·0, 25·0–29·9 and ≥30 kg/m^2). Adults with a BMI of 25·0–29·9 kg/m^2 were considered to be overweight and those with a BMI ≥30 kg/m^2 were defined as being obese.

Participants in the low education category did not proceed beyond secondary school; the high education category included subjects admitted to college or university, as well as those with a post-secondary school certificate or diploma. Subjects were classified into low- (<\$50 000) and high-income (≥\$50 000) groups based on total household income. Current smokers were participants who reported smoking every day or almost every-day, and had smoked at least twenty packs during their lifetime. Ex-smokers were those who were regular smokers but, at the time of the survey, had quit for at least 6 months. A regular drinker was defined as a person who drank alcoholic beverages at least once per week, on average.

The relationships between BMI, family history and diabetes were examined among 2081 adults aged 18–79 years, who provided information on BMI, family history and diabetes. We calculated the prevalence of diabetes according to various risk factors. Log-binomial regression model was used to estimate unadjusted and adjusted prevalence ratio (PR) for associations among BMI, family history and diabetes[24]. The maximum likelihood estimations of PR were obtained and likelihood ratio CI were used for statistical inference. We also used a log-binomial regression model to evaluate the departures from additivity after adjustment for potential confounders. Indicator terms from each category of joint exposure were constructed

in the model. People who were exposed neither to overweight/obesity nor to family history were defined as the reference category. Five indicator terms dealing with the joint effects of overweight/obesity and family history were built into the model. They indicate either the presence of each exposure and the absence of the other or the presence of joint exposure. We used the method developed by Zou[25] to estimate the additive effect of family history and BMI on the prevalence of diabetes. Relative excess risk of interaction (RERI), attributable proportion of interaction and Rothman's synergy index were calculated to access deviation from the additive model[25].

Results

There were more female than male participants, 56 % *v.* 44 %. The participants had an average age of 51·9 (SD 15·8) years. The prevalence of doctor-diagnosed diabetes was 7·9 % in adults aged 18–79 years. Table 1 shows the characteristics of the study population associated with the prevalence of diabetes. Age, socio-economic status, smoking and alcohol drinking were significantly associated with the crude prevalence of diabetes.

The prevalence increased significantly with BMI (Table 2). Of the participants, 23·0 % of the participants reported that at least one of their parents had diabetes and 12·5 % reported that at least one of their siblings had the disease. Overall, 29·7 % of the subjects had one or more diabetic parents or siblings. The prevalence of doctor-diagnosed diabetes was significantly higher among those with a family history of diabetes compared with those without (Table 2).

Table 1 Prevalence of diabetes according to characteristics of the study population 18–79 years of age, the Humboldt Study, 2003

	n	Cases	%	χ^2 (*P* value)
Age (years)				
18–39	513	11	2·1	
40–59	808	41	5·1	81·23 (<0·001)
60–79	760	112	14·7	
Sex				
Male	906	77	8·7	0·84 (0·358)
Female	1175	87	7·4	
Educational level				
Low	1113	103	9·3	
High	931	55	5·9	11·43 (0·003)
Unknown	37	6	16·7	
Income				
Low	846	80	9·5	
High	769	42	5·5	9·91 (0·007)
Unknown	466	42	9·0	
Smoking status				
Non-smoker	1103	77	7·0	
Ex-smoker	719	72	10·0	7·29 (0·026)
Smoker	259	15	5·8	
Alcohol use				
No	826	99	12·0	
Yes	1232	65	5·2	31·81 (<0·001)
Unknown	23	1	4·4	

Table 2 Prevalence of diabetes associated with BMI and family history in adults 18–79 years of age, the Humboldt Study, 2003

	n	Cases	%	χ^2 (P value)
BMI (kg/m^2)				
<25	565	20	3·5	
25·0–29·9	779	55	7·1	33·26 (<0·001)
≥30	737	89	12·1	
Parent with diabetes				
No	1603	97	6·1	32·18 (<0·001)
Yes	478	67	14·0	
Sibling with diabetes				
No	1821	102	5·6	104·32 (<0·001)
Yes	260	62	23·8	
Parent or sibling with diabetes				
No	1462	71	4·9	61·93 (<0·001)
Yes	619	93	15·0	

Table 3 Unadjusted and adjusted* prevalence ratios (PR) and 95 % CI for diabetes in relation to BMI and family history in adults 18–79 years of age, the Humboldt Study, 2003

	Unadjusted		Adjusted	
	PR	95 % CI	PR	95 % CI
BMI (kg/m^2)				
<25·0	1·00		1·00	
25·0–29·9	1·99	1·23, 3·37	1·76	1·37, 2·27
≥30·0	3·41	2·17, 5·63	2·59	2·05, 3·31
Family history of diabetes				
Parent	2·32	1·72, 3·10	2·11	1·83, 2·44
Sibling	4·26	3·18, 5·66	2·73	2·39, 3·11
Parent or sibling	3·09	2·31, 4·17	2·41	2·08, 2·80

*Adjusted for age, alcohol drinking and family history for BMI associated with diabetes, and adjusted for age, alcohol drinking and BMI for family history associated with diabetes.

Fig. 1 Prevalence of diabetes by family history and BMI in adults aged 18–79 years (□, normal; ▨, overweight; ▪, obese)

Table 4 Adjusted* prevalence ratios (PR) and 95 % CI for the combined effects of BMI and family history on diabetes in adults 18–79 years of age, the Humboldt Study, 2003

	Parent or sibling with diabetes			
	No		Yes	
BMI (kg/m^2)	PR	95 % CI	PR	95 % CI
<25·0	1·00		2·29	1·45, 3·62
25·0–29·9	1·43	0·97, 2·19	4·73	3·24, 6·94
≥30·0	2·83	2·01, 4·14	5·70	3·98, 8·17

*Adjusted for age and alcohol drinking.

A logistic regression model was first utilised to assess the impact of BMI, family history and individual characteristics on diabetes. Non-significant variables including sex, education, income and smoking status were excluded from further analysis. A log-binomial regression model was then used to assess the independent effect of BMI and family history on the prevalence of doctor-diagnosed diabetes. After controlling for age, alcohol drinking and family history, the adjusted PR for those with a BMI of at least 30 kg/m^2 and a BMI of 25·0–29·9 kg/m^2, compared with a BMI of less than 25 kg/m^2, was 2·59 (95 % CI 1·05, 3·31) and 1·76 (95 % CI 1·37, 2·27), respectively (Table 3). After controlling for age, alcohol drinking and BMI, the adjusted PR was 2·41 (95 % CI 2·08, 2·80) for those with a family history compared with those without (Table 3).

Figure 1 shows that the prevalence of doctor-diagnosed diabetes increased with BMI more rapidly in those with a family history of diabetes than those without a family history. It seems that those with a family history are more susceptible to diabetes due to overweight/obesity.

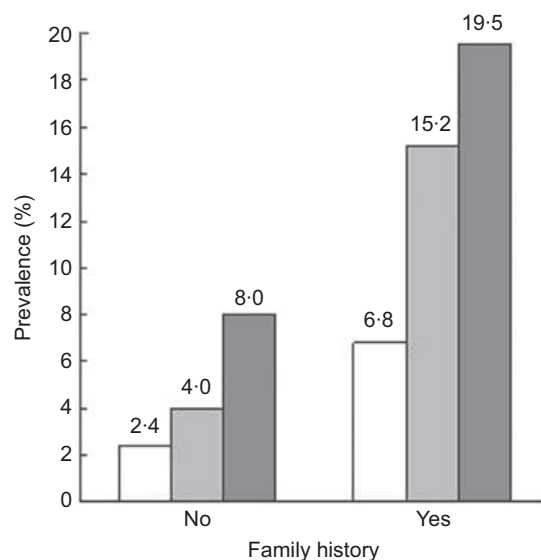A log-binomial regression model was used to evaluate the departures from additivity for BMI and family history associated with diabetes, after adjustment for age and alcohol drinking. The risk of diabetes was approximately three-fold higher for those who either had family history or were obese before adjustment (Table 4). For those who had both family history and obesity, the PR was 5·70 (95 % CI 3·98, 8·17; Table 4). The RERI was 1·92, and 85 % of the diabetes risk was attributed to the synergy between overweight/obesity and family history. The combined effect of overweight/obesity and family history accounted for 36 % of those subjects who developed diabetes.

Discussion

Obesity is a major determinant of type 2 diabetes, and a number of studies have confirmed the association between obesity and type 2 diabetes[26]. BMI, waist circumference and waist-to-hip ratio are all associated with type 2 diabetes[27]. Based on data from thirty-two studies, the pooled relative risks for incident diabetes were 1·87 (95 % CI 1·67, 2·10), 1·87 (95 % CI 1·58, 2·20) and 1·88 (95 % CI 1·61, 2·19) per sd of BMI, waist circumference and waist-to-hip ratio[27]. A combined analysis of twenty-seven studies from the Asia Pacific region, which included

154 989 subjects with 1 244 793 person-years of follow-up, has shown that each $2\,kg/m^2$ reduction of BMI is associated with a 27 % (23–30 %) lower risk of diabetes[28]. Lost weight after gastric bypass surgery reduces the risk of diabetes[26].

It is clear that obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. In obese individuals, adipose tissue releases increased amounts of NEFA, glycerol, hormones, adiponectin, resistin, TNF-α and IL-6, and results in an impairment of insulin sensitivity, development of insulin resistance and dysfunction of pancreatic islet β-cells[15,16].

Family history of diabetes has been recognised as an important risk factor for diabetes. Family history of diabetes is significantly associated with the risk of diabetes[2,29] and has an exponential impact on ageing-associated increase in the risk of diabetes[30]. Our study indicated that family history was associated with a higher risk of diabetes in adults 18–79 years of age. Siblings' status of diabetes tended to have a greater impact on the prevalence of diabetes than that of parents, but the difference was not statistically significant. They were merged in the analysis of interaction with overweight/obesity.

It has been found that declines in insulin sensitivity and in the disposition index, and increases in fasting glucose are significantly influenced by a maternal history of type 2 diabetes[31]. In children, family history of type 2 diabetes is associated with decreased insulin sensitivity and clearance[8].

Although there is strong evidence for both family history and obesity being important determinants of type 2 diabetes, it has not been well understood if family history and obesity synergistically influence diabetes. In an earlier cross-sectional study of 3128 men and 4821 women aged 35–56 years, combined exposure to a family history of diabetes and lifestyle-related risk factors, including obesity, had a greater effect on type 2 diabetes than any of these factors alone. The additive interaction was statistically significant for a family history of diabetes and obesity in women with prediabetes, but not in others[4]. In our study, we asked questions about family history of their biological father, mother and siblings and one-third of the study population had at least one of the relatives having the disease. The synergistic effect of family history and overweight/obesity was statistically significant, indicated by the indices of synergism.

The mechanisms for possible synergistic influence of a family history of diabetes and obesity on prevalent type 2 diabetes need to be further explored. Family history scores based on the diabetes status of the participants' parents and older siblings were found to be significantly correlated with reduced insulin sensitivity and increased subcutaneous and visceral fat in families from San Antonio and Los Angeles, but not in the leaner Hispanic families from San Luis Valley[32]. The authors of the study believed that the lack of an association between family history score and insulin resistance/fat accumulation in leaner families is likely due to a suppression of the expression of transmitted diabetes genes in leaner, more physically active populations[32]. If this speculation is true, it may explain our observation that family history has a larger influence on diabetes in the overweight/obese than normal weight populations.

There are several limitations for the study. First, it is a cross-sectional study and we are not able to make any firm inclusion about causality. Second, the study is relatively small and only limited variables are included in the log-binomial regression model. This approach allowed us to produce PR estimates and to provide more accurate estimates for BMI and family history synergism. Third, the diagnosis of diabetes was self-reported, although validated questions were used in the survey.

Since type 2 diabetes poses substantial burdens of medical care and financial resources for individual patients, their families and society as a whole, prevention and control of the disease is of great importance. Family history represents valuable information on genetic and common environmental exposures. Family history can be a useful screening tool to identify people at high risk for diabetes[5,29,33] and is considered as a promising public health tool to fight the growing epidemic of diabetes[34]. The validity and utility of using family history as a screening tool can be largely improved by combining with BMI or other measures of adiposity, which will help in identifying high-risk groups and developing targeted intervention programmes.

Acknowledgements

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