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Association between parental history of diabetes and the incidence of type 2 diabetes mellitus differs according to the sex of the parent and offspring's body weight: A finding from a Japanese worksite-based cohort study

Chaochen Wang [a,c], Hiroshi Yatsuya [a,b,*], Koji Tamakoshi [d], Hideaki Toyoshima [e], Keiko Wada [f], Yuanying Li [b], Esayas Haregot Hilawe [a], Mayu Uemura [a,g], Chifa Chiang [a], Yan Zhang [a], Rei Otsuka [h], Atsuhiko Ota [b], Yoshihisa Hirakawa [a], Atsuko Aoyama [a]

[a] Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine, Nagoya, Japan
[b] Department of Public Health, Fujita Health University School of Medicine, Toyoake, Aichi, Japan
[c] Department of Public Health, Aichi Medical University School of Medicine, Nagakute, Aichi, Japan
[d] Department of Nursing, Nagoya University School of Health Science, Nagoya, Japan
[e] Education and Clinical Research Training Center, Anjo Kosei Hospital, Anjo, Aichi, Japan
[f] Department of Epidemiology and Preventive Medicine, Gifu University Graduate School of Medicine, Gifu, Japan
[g] Department of Epidemiology, Fukushima Medical University School of Medicine, Fukushima, Japan
[h] Section of Longitudinal Study of Aging, National Institute for Longevity Sciences (NILS-LSA), National Center for Geriatrics and Gerontology, Obu, Aichi, Japan

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ABSTRACT

Objective. To investigate differences in the association of parental history of diabetes with the risk of type 2 diabetes mellitus (T2DM) in the offspring according to the sex of the parent and the offspring's body weight.

Methods. A prospective cohort study of 4446 middle-aged non-diabetic Japanese men and women were followed in Aichi Prefecture, central Japan, from 2002 to 2011. Subjects were categorized by their self-reported parental history of diabetes ("no parental history," "father only," "mother only," and "both"). The association of parental history of diabetes and incidence in the offspring was examined according to overweight status adjusted for age, sex, birth weight, smoking, alcohol consumption, physical activity, total energy intake, body mass index, and number of metabolic syndrome components.

Results. During follow-up (median 8.9 years), 277 subjects developed T2DM. Parental history of diabetes was positively associated with T2DM incidence. However, stratified analysis by overweight status revealed that only maternal history was associated with increased T2DM incidence in non-overweight subjects (hazard ratio = 2.35, 95% confidence interval: 1.41–3.91). While in overweight subjects, paternal history was significantly associated with higher T2DM incidence (hazard ratio = 1.98, 95% confidence interval: 1.19–3.28).

Conclusions. Our results suggest that parental history of diabetes mellitus is associated with the incidence of T2DM in offspring differently according to the sex of the affected parent and the offspring's body weight.

Introduction

Obesity is a well-known risk factor for type 2 diabetes mellitus (T2DM) development (Ardisson Korat et al., 2014). However, some non-obese individuals develop T2DM, suggesting the existence of a familial influence (Paolo, 2007; Vaag and Lund, 2007). Indeed, family history was more strongly associated with diabetes prevalence in non-overweight individuals than in the overweight or obese in US blacks and Hispanics, but not in whites (Suchindran et al., 2009). Although the finding indicated existence of higher genetic influence in lean non-white populations, the issue has not been explored in other ethnicities, particularly in prospective studies. In addition, some previous studies have indicated a stronger maternal-offspring association with T2DM compared with the paternal-offspring association (Alcolado et al., 2002; Lin et al., 1994; Sakurai et al., 2013; Thorand et al., 2001). Therefore, it would be relevant to examine the association of a parental history of diabetes with T2DM risk in the offspring according to the sex of the parent and the offspring's body weight.

Furthermore, it is well known that one's weight could decrease or fluctuate due to his/her worsened glycemic control. Alternatively, it is also possible for the weight to increase during the follow-up before

* Corresponding author at: Department of Public Health, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan.
E-mail address: yatsuya@gmail.com (H. Yatsuya).

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the onset of diabetes. Taking only baseline weight status may not be appropriate because it might lead to complex misclassification especially in dealing with diabetes.

Accordingly, in a worksite-based cohort of middle-aged Japanese men and women, we investigated the association of parental history of diabetes with T2DM risk in the offspring according to the sex of the parents and the offspring's body weight, which was longitudinally collected by mandatory annual health check-up at the worksite.

Methods

Subjects

In 2002, 6648 civil servants employed in a local government office in Japan responded to a baseline survey using a self-administered questionnaire. In total, 5471 subjects provided information about their medical and family history of certain diseases, diet, and lifestyle, and gave written informed consent to the use of their mandatory annual health check-up data in this study. We excluded subjects with missing baseline information on BMI, smoking status, alcohol consumption, and physical activity ($n = 374$); prevalent diabetes, defined as self-reported medication use or baseline glucose levels ≥126 mg/dL ($n = 651$). Finally, 4446 subjects (3492 men and 954 women) were left for the present analysis. Subjects were followed until the end of March 2011. Those who retired after the age of 60 were contacted by mail ($n = 743$).

The study protocol was approved by the Bioethic Review Committee of Nagoya University School of Medicine, Nagoya, Japan.

Ascertainment of T2DM incidence

T2DM incidence was ascertained by two methods. First, participants' mandatory annual health check-up data from 2002 to 2011 were reviewed. Incidence was defined as the year when fasting glucose levels first reached ≥126 mg/dL. Second, subjects reported detailed medical histories of several pre-specified conditions including T2DM in approximately biennial self-administered questionnaire surveys carried out between 2004 and 2011. The year of diabetes diagnosis was also reported and we requested contact details for the physician (present or past) in charge of the disease management. The accuracy of self-reports (95%) for those who provided consent in a validation study has been reported elsewhere (Wada et al., 2009). All of the self-reported T2DM cases (with or without validation) were included in the present analysis.

Anthropometric measurements and biochemical analysis

Weight and height were measured with the subjects in light indoor clothing and without shoes to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated as weight (kg) divided by the square of height (m). Blood pressure was measured with the subjects in a seated position after a minimum of 5 minutes' rest. Blood samples were collected 8 h after the last meal or an overnight fast. Serum was isolated immediately and routine health check-up factors including levels of fasting blood glucose, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured. Metabolic syndrome components were defined by minimally modified Adult Treatment Panel III (ATP-III) criteria (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), 2002): (1) BMI ≥25 kg/m^2; (2) HDL-C <40 mg/dL in men, <50 mg/dL in women; (3) TG ≥150 mg/dL or treatment for hyperlipidemia; (4) fasting glucose ≥110 mg/dL; (5) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or taking antihypertensive medication. Subjects with three or more of the above abnormalities at baseline were considered as having metabolic syndrome.

Smoking status was categorized as current, former, and never. Physical activity was assessed by a questionnaire item, "Do you engage in leisure-time physical activity regularly (at least one day per month and 60 minutes in total)?" We have adjusted yes response to this item in the multivariate model. A brief self-administered dietary history questionnaire (Kobayashi et al., 2011, 2012) was used to assess alcohol consumption (days per week) and total energy intake per day (kcal/day). Subjects were asked to describe their birth weight according to the following categories: less than 2500 grams (g); 2500–3000 g; 3000–3500 g; 3500–4000 g; higher than 4000 g, and unknown. In Japan, the Maternal and Child Health Handbook is provided to all pregnant women per each baby by their local government by law which is used as a birth certificate after delivery. The handbook is filled in by the obstetrician or midwife for birth weight information. It also contains important information relevant to pregnancy and birth as well as child development. It will be used through adolescence since it includes coupons and schedules for vaccinations. Thus, we considered self-reported birth weight data to be valid.

Statistical analyses

Parental history of diabetes was categorized as follows: "no parental history," "father only," "mother only," and "both." Age- and sex-adjusted means and proportions of potential confounding factors across the categories were compared using a general linear model. T2DM incidence rates were calculated by Poisson regression adjusted for age and sex. Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the T2DM risk among subjects in each category taking the "no parental history" as the reference. Model 1 adjusted for age, sex, smoking status, alcohol consumption, birth weight categories, physical activity (yes/no), and total energy intake. Model 2 included the covariates in Model 1 plus BMI. Model 3 included the covariates in Model 2 plus the number of metabolic syndrome components (0–5).

It is possible for previously overweight or obese subjects to lose weight during the course of disease development before it becomes overt; therefore, we carried out two sensitivity analyses restricted to (1) subjects continuously non-overweight from baseline to the end of follow-up and to (2) subjects continuously non-overweight from young adulthood. Weight at 20, 25, 30, 35, 40 years of age and 5 years before baseline were self-reported. We have reported the validity of recalled weight at approximately age 25 previously (Tamakoshi et al., 2003). Weights from baseline to the end of follow-up were obtained during annual health check-ups.

Multiplicative interaction tests were performed using the likelihood ratio test, comparing the fit of models with a cross-product term between parental history categories and the BMI with that of models without this term. Statistical analyses were conducted with R version 3.1.2 (2014-10-31) (R Core Team, 2014), packages of Epicalc (Chongsuvivatwong, 2008) and Survival (Therneau, 2013; Therneau and Grambsch, 2000). All *P*-values are two-sided, and *P*-values of less than 0.05 were considered to indicate statistical significance.

Results

The mean (standard deviation, SD) age and BMI at baseline were 47.5 (7.1) years and 22.9 (2.8) kg/m^2, respectively. Of the 4446 subjects, 614 (13.8%) reported a history of diabetes in at least one parent at baseline. Table 1 shows baseline characteristics of the subjects according to the parental history categories. Smoking status, physical activity, alcohol consumption, fasting glucose, systolic blood pressure, total energy intake and levels of total cholesterol, TG, and HDL-C, as well as the prevalence of metabolic syndrome did not differ significantly according to the parental history of diabetes. Whereas means of age BMI, and diastolic blood pressure, percentage of men, and low self-reported birth weight were statistically significantly different among parental history categories.

During follow-up (median 8.9 years), 277 subjects developed T2DM (227 men and 50 women), with an annual incidence rate of 7.9 per 1000 person-years. The age- and sex-adjusted annual incidence rate was highest in the "both parents" category (25.7 per 1000 person-years) and lowest in the "no parental history" category (7.0 per 1000 person-years). Compared with a negative parental history, subjects in the "father only," "mother only," or "both parents" categories exhibited significantly higher risk of T2DM (Table 2). The corresponding multivariable-adjusted HRs and 95% CIs in Model 3 were 1.72 (1.19–2.47), 1.66 (1.07–2.58), and 3.46 (1.42–8.43) for the "father only," "mother only," or "both parents" categories, respectively. However, stratified analysis by subjects' classification as overweight at baseline revealed a statistically significant association of "mother only" history with T2DM incidence only in the non-overweight group (HR: 2.35, 95% CI: 1.41–3.91) and not in the overweight group (HR: 0.84, 95% CI: 0.34–2.08). In contrast, subjects in the "father only" category were associated with a higher risk of T2DM only in the overweight group (HRs: 1.52 (0.89–2.62) and 1.98 (1.19–3.28) in the non-overweight and