



Associations of parental history of diabetes mellitus with the offspring's incidence is modified by offspring's body weight, findings from a Japanese work-site based cohort

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INTRODUCTIONS

- ◆ Family history may reflect complex relationships between genetic factors and environmental conditions that are important for developing diabetes.
- ◆ A greater risk from maternal history of diabetes compare to paternal history has been reported in some, but not in all studies.
- ◆ Cross-sectional report from the same population of our cohort study found that maternal history of hypertension, diabetes and dyslipidemia were more strongly associated with off-spring's prevalence of metabolic syndrome than paternal history.¹
- ◆ Proposed explanations included following:
 - Mutations of mitochondrial DNA;
 - Intrauterine environment;
 - Behavior influence of the mother;
- ◆ It has been hypothesized that interactions between genetic- and environmental factors are of specific importance for the development of type 2 diabetes (T2D).
- ◆ Previous study indicated that obesity may significantly modify the association between parental history of diabetes and risk of new incidence.²

OBJECTIVES

In the current worksite-based Japanese cohort study:

- ① The difference in the risk of T2D between individuals with paternal- and maternal history of diabetes was investigated;
- ② The interaction effect of overweight on this association was tested.

METHODS

Participants:

5,471 workers (4,299 men; 1,172 women)

Exclusions:

- ① History of diabetes (n = 430)
- ② Baseline fasting blood glucose higher or equal to 126 mg/dL or self-reported under treatment of T2D (n = 221)
- ③ Body mass index (BMI), sex, smoking and drinking status, physical activity not available (n = 374)

n = 4,446 (3,492 men; 954 women)

Follow-ups: from May 2002 until April 2011

Diagnosis of T2D:

- ① Fasting glucose measured in the annual health check-up first exceeded 126 mg/dL;
- ② Self-reported in the questionnaires sent every 2 years during the follow-up. And confirmed by the physician in charge for the date of diagnosis.

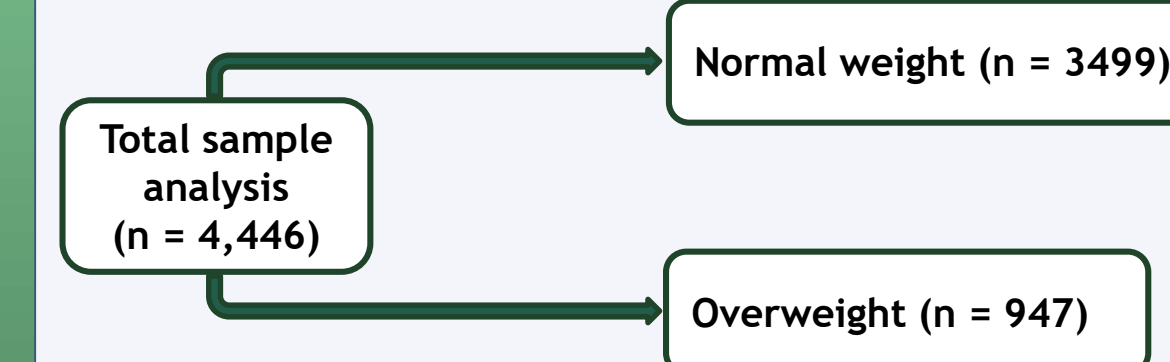
Other data collections including:

- ① Parental history of diabetes and categorized as: None, Father-only, Mother-only or Both;
- ② BMI was calculated from the weight and height measured during the annual health check-ups from 2002 through the year of 2011, the baseline value was applied for primary analysis, by utilizing the formula (weight, kg) ÷ (height, m)²; Overweight was defined as BMI higher or equal to 25 kg/m²;
- ③ Smoking status (current, past, never);
- ④ Alcohol consumption (times/week);
- ⑤ Physical activity was defined as participation of moderate or vigorous leisure-time exercise for at least 12 days/month or more than 360 min/moth in total (yes or no);

METHODS cont.

Statistical analysis:

- Baseline descriptive statistics of the participants were reported as mean ± standard deviation (SD) and groups were compared using analysis of variance or ² test;
- Incidence rate of T2D during the follow-up was evaluated by Poisson regression adjusted for age, sex, smoking status, alcohol consumption, BMI and physical activity;
- Multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated including the same above covariates by Cox proportional hazard model taking the category of "None" for parental history as the reference group in the total sample analysis;
- Another analyses was performed:
 - HRs of T2D incidence according to the presence of paternal or maternal history of diabetes;
 - Stratified by overweight.



- Likelihood ratio test was used to test the interaction effect of overweight.

RESULTS

Table 1. Means (SD) and percentages of the participants at baseline, Aichi, 2002.

| | Neither | Father | Mother | Both | P value |
|---|--------------------|--------------------|--------------------|---------------------|---------|
| n | 3,832 | 373 | 216 | 25 | |
| Age (SD), years | 47.7 (7.1) | 45.9 (6.8) | 48.4 (6.8) | 46.1 (6.5) | < 0.001 |
| Men, % | 79.5 | 71.3 | 73.6 | 80.0 | < 0.001 |
| Body mass index (SD), kg/m ² | 22.9 (2.8) | 23.4 (2.9) | 23.5 (2.8) | 23.4 (2.8) | < 0.001 |
| Current smoker, % | 28.6 | 28.7 | 22.7 | 36.0 | 0.37 |
| Presence of physical activity, % | 55.6 | 52.0 | 58.8 | 56.0 | 0.42 |
| Alcohol consumed everyday, % | 30.8 | 24.3 | 28.2 | 32.0 | 0.27 |
| Fasting glucose, geometric mean, (95% CI) | 92.3 (91.9 - 92.6) | 92.2 (91.2 - 93.3) | 93.5 (92.1 - 94.9) | 95.7 (91.3 - 100.2) | 0.11 |

RESULTS cont.

- During the median of 8.9 years follow-up, 277 cases of T2D (227 men, 50 women) developed;
- Multivariable adjusted incidence rate: 7.9 per 1,000 person-year;

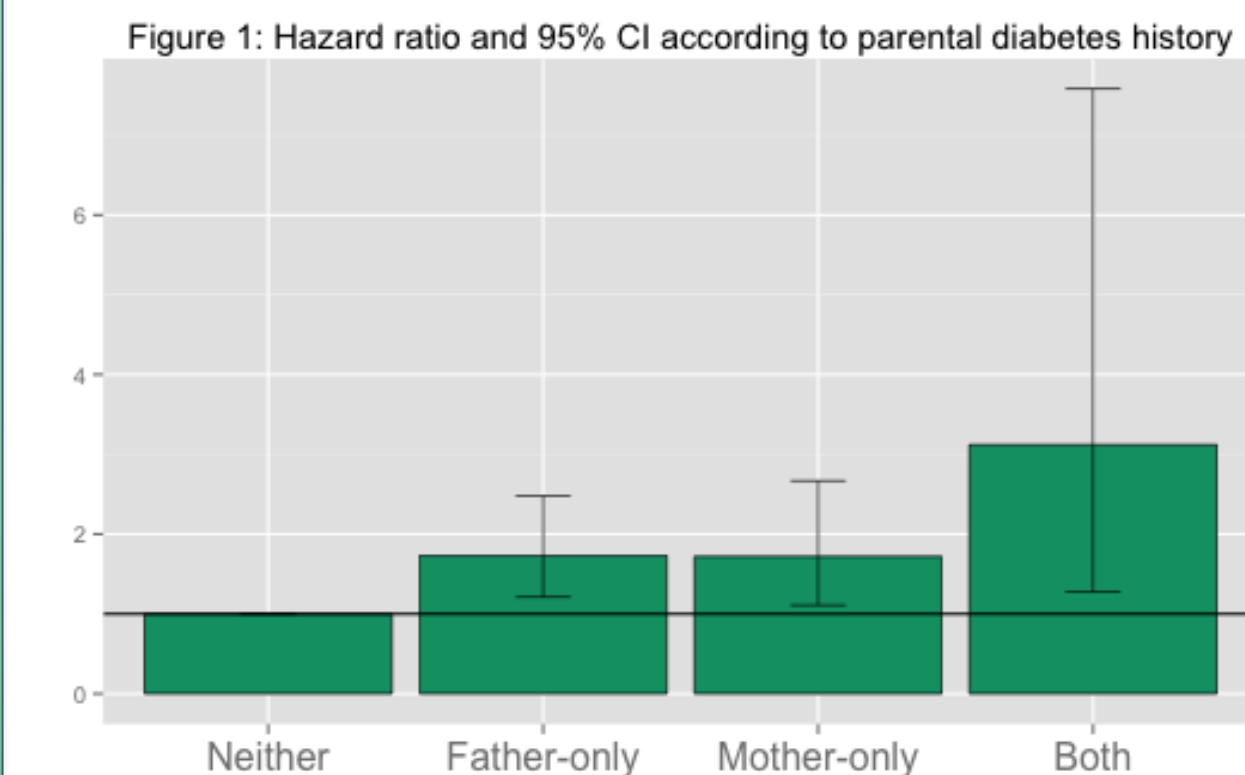


Table 2. Hazard ratios (95% CIs) according to parental history of diabetes stratified by overweight.

| | Total (n = 4,446) | | Normal weight (n = 3,499) | | Overweight (n = 947) | | P for interaction |
|--------------------|-------------------|--------------------|---------------------------|--------------------|----------------------|--------------------|-------------------|
| | IR* | HR (95% CI) | IR* | HR (95% CI) | IR* | HR (95% CI) | |
| Maternal history - | 6.7 | 1 | 5.2 | 1 | 14.2 | 1 | 0.017 |
| Maternal history + | 11.8 | 1.79 (1.20 - 2.67) | 13.2 | 2.57 (1.61 - 4.12) | 12.8 | 0.86 (0.40 - 1.86) | |
| Paternal history - | 6.6 | 1 | 5.4 | 1 | 12.9 | 1 | 0.485 |
| Paternal history + | 10.9 | 1.76 (1.26 - 2.47) | 8.2 | 1.59 (0.97 - 2.60) | 22.3 | 1.92 (1.19 - 3.08) | |

*IR, incidence rate

Findings:

- ① Parental histories (father-only, mother-only, or both) of diabetes were positively associated with T2D incidence in middle-aged male and female workers in Japan.
- ② Maternal history of diabetes increased the risk of T2D in normal weight subjects to a degree that was observed in overweight subjects without parental history.
- ③ Being Overweight significantly increased the risk of T2D in subjects with paternal diabetes history.

DISCUSSIONS

Potential explanations:

- Genomic imprinting, regulatory regions of certain genes are differentially methylated and expressed depending on whether the gene is inherited from the mother or father and may also interact with offspring's BMI.³
- Maternal effects on the intrauterine environment on fetal development (including perinatal nutrition, and metabolism), and epigenetic modifications in oocytes (both nuclear and mitochondrial DNA methylation) may contribute to the maternal transmission of diabetes in normal weight subjects.

Limitations:

- Self-reported information might had recall bias
- Baseline information were not updated (BMI, parental DM might change during the follow-up), further confirmation needed.
- Incidence ascertainment was through annual health check-up and self-reported. Validation was done by reviewing the medical records with consent (38%).
- We do not have the information about age of diagnosis of the subjects parents.

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