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23 van den Berg E, Dekker JM, Nijpels G, Kessels RP, Kappelle LJ, de Haan EH, Heine RJ, Stehouwer CD, Biessels GJ: Cognitive functioning in elderly persons with type 2 diabetes and metabolic syndrome: the Hoorn study. Dement Geriatr Cogn Disord 2008;26:261–269.
24 Qiu WQ, Price LL, Hibberd P, Buell J, Collins L, Leins D, Mwamburi DM, Rosenberg I, Smaldone L, Scott TM, Siegel RD, Summergrad P, Sun X, Wagner C, Wang L, Yee J, Tucker KL, Folstein M: Executive dysfunction in homebound older people with diabetes mellitus. J Am Geriatr Soc 2006;54:496–501.
25 Fischer AL, de Frias CM, Yeung SE, Dixon RA: Short-term longitudinal trends in cognitive performance in older adults with type 2 diabetes. J Clin Exp Neuropsychol 2009;31:809–822.
26 Abbatecola AM, Paolisso G, Lamponi M, Bandinelli S, Lauretani F, Launer L, Ferrucci L: Insulin resistance and executive dysfunction in older persons. J Am Geriatr Soc 2004;52:1713–1718.
27 Cukierman-Yaffe T, Gerstein HC, Williamson JD, Lazar RM, Lovato L, Miller ME, Coker LH, Murray A, Sullivan MD, Marcovina SM, Launer LJ: Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: the action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial; Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) Investigators. Diabetes Care 2009;32:221–226.
28 Vanhanen M, Koivisto K, Kuusisto J, Mykkänen L, Helkala EL, Hänninen T, Riekkinen P Sr, Soininen H, Laakso M: Cognitive function in an elderly population with persistent impaired glucose tolerance. Diabetes Care 1998;21:398–402.
29 Geroldi C, Frisoni GB, Paolisso G, Bandinelli S, Lamponi M, Abbatecola AM, Zanetti O, Guralnik JM, Ferrucci L: Insulin resistance in cognitive impairment: the inCHIANTI study. Arch Neurol 2005;62:1067–1072.
30 Hallschmid M, Schultes B: Central nervous insulin resistance: a promising target in the treatment of metabolic and cognitive disorders? Diabetologia 2009;52:2264–2269.
31 Welsh B, Wecker L: Effects of streptozotocin-induced diabetes on acetylcholine metabolism in rat brain. Neurochem Res 1991;16:453–460.
32 Kamal A, Biessels GJ, Urban IJ, Gispen WH: Hippocampal synaptic plasticity in streptozotocin-diabetic rats: impairment of long-term potentiation and facilitation of long-term depression. Neuroscience 1999;90:737–745.
33 Jokinen H, Kalska H, Ylikoski R, Madureira S, Verdelho A, van Der Flier WM, Scheltens P, Barkhof F, Visser MC, Fazekas F, Schmidt R, O'Brien J, Waldemar G, Wallin A, Chabriat H, Pantoni L, Inzitari D, Erkinjuntti T; LADIS group: Longitudinal cognitive decline in subcortical ischemic vascular disease – the LADIS Study. Cerebrovasc Dis 2009;27:384–391.
34 Turken A, Whitfield-Gabrieli S, Bammer R, Baldo JV, Dronkers NF, Gabrieli JD: Cognitive processing speed and the structure of white matter pathways: convergent evidence from normal variation and lesion studies. Neuroimage 2008;42:1032–1044.
35 Umegaki H, Kawamura T, Mogi N, Umemura T, Kanai A, Sano T: Glucose control levels, ischaemic brain lesions, and hyperinsulinaemia were associated with cognitive dysfunction in diabetic elderly. Age Ageing 2008;37:458–461.
36 Herrmann LL, Goodwin GM, Ebmeier KP: The cognitive neuropsychology of depression in the elderly. Psychol Med 2007;37:1693–1702.
37 Santos M, Kövari E, Hof PR, Gold G, Bouras C, Giannakopoulos P: The impact of vascular burden on late-life depression. Brain Res Rev 2009;62:19–32.
38 Compeán-Ortiz LG, Gallegos EC, Gonzalez-Gonzalez JG, Gomez-Meza MV, Therrien B, Salazar BC: Cognitive performance associated with self-care activities in Mexican adults with type 2 diabetes. Diabetes Educ 2010;36:268–275.

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# A cross-sectional study of glucose regulation in young adults with very low birth weight: impact of male gender on hyperglycaemia

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## ABSTRACT

**Objectives:** To investigate glucose regulation in young adults with very low birth weight (VLBW; <1500 g) in an Asian population.

**Design:** Cross-sectional observational study.

**Setting:** A general hospital in Hamamatsu, Japan.

**Participants:** 111 young adults (42 men and 69 women; aged 19–30 years) born with VLBW between 1980 and 1990. Participants underwent standard 75 g oral glucose tolerance test (OGTT).

**Primary and secondary outcome measures:** The primary outcomes were glucose and insulin levels during OGTT and risk factors for a category of hyperglycaemia defined as follows: diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting glycaemia (IFG) and non-diabetes/IGT/IFG with elevated 1 h glucose levels (>8.6 mmol/l). The secondary outcomes were the pancreatic β cell function (insulinogenic index and homeostasis model of assessment for beta cell (HOMA-β)) and insulin resistance (homeostasis model of assessment for insulin resistance (HOMA-IR)).

**Results:** Of 111 young adults with VLBW, 21 subjects (19%) had hyperglycaemia: one had type 2 diabetes, six had IGT, one had IFG and 13 had non-diabetes/IGT/IFG with elevated 1 h glucose levels. In logistic regression analysis, male gender was an independent risk factor associated with hyperglycaemia (OR 3.34, 95% CI 1.08 to 10.3, p=0.036). Male subjects had significantly higher levels of glucose and lower levels of insulin during OGTT than female subjects (p<0.001 for glucose and p=0.005 for insulin by repeated measures analysis of variance). Pancreatic β cell function was lower in men (insulinogenic index: p=0.002; HOMA-β: p=0.001), although no gender difference was found in insulin resistance (HOMA-IR: p=0.477). In male subjects, logistic regression analysis showed that small for gestational age was an independent risk factor associated with hyperglycaemia (OR 33.3, 95% CI 1.67 to 662.6, p=0.022).

**Conclusions:** 19% of individuals with VLBW already had hyperglycaemia in young adulthood, and male

## ARTICLE SUMMARY

### Article focus

- Neonatal intensive care has improved the survival rate for very low birth weight infants (VLBW; birth weight <1500 g) in recent decades, and the first generation of VLBW infants have only recently reached young adulthood.
- Only a few studies have shown that VLBW (or preterm) is associated with glucose intolerance in Caucasian young adults, while glucose regulation in Asian young adults with VLBW is still uncertain.
- The present study investigated glucose regulation in young adults with VLBW in an Asian population and determined the factors associated with hyperglycaemia.

### Key messages

- Of 111 young adults with VLBW, 19% of individuals already had hyperglycaemia (type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glycaemia (IFG) and non-diabetes/IGT/IFG with elevated 1 h glucose levels).
- Male gender was a significant independent risk factor of hyperglycaemia in young adults with VLBW.
- Small for gestational age was associated with hyperglycaemia particularly in male young adults with VLBW.

### Strengths and limitations of this study

- This is the first study assessing the glucose regulation in young adults with VLBW in an Asian population.
- This study does not provide information on postnatal growth patterns, which have been shown to be associated with later hyperglycaemia in previous studies.
- The study design with no control subjects makes it impossible to address the delayed impact of VLBW itself on glucose regulation.

gender was a significant independent risk factor of hyperglycaemia. In male young adults with VLBW, small for gestational age was associated with hyperglycaemia.

## INTRODUCTION

In recent decades, progression of neonatal intensive care has dramatically increased the survival rate of very low birth weight (VLBW; birth weight <1500 g) infants worldwide.[1] A lot of them have grown up into young adults (now in their 20s or 30s). To date, epidemiological studies have shown an association between low birth weight and type 2 diabetes and cardiovascular disease in later life.[2–4] Fetal malnutrition in the gestational period, which prevents appropriate fetal growth in utero, is thought to provoke thrifty phenotype in premature babies. This phenotype is assumed to predispose them to subsequent metabolic disorders. For this reason, to foresee the later risk of type 2 diabetes is very crucial for VLBW infants, which would lead to prevention of type 2 diabetes by early intervention in their lifestyle.[5–7]

The first generation of VLBW infants have only recently reached young adulthood. A few studies have shown that VLBW (or preterm) is associated with glucose intolerance in young adulthood in Caucasian populations,[8 9] while the glucose regulation in Asian young adults with VLBW remains uncertain. To clarify the characteristics of glucose metabolism in young adults with VLBW in an Asian population, we investigated glucose regulation in 111 young adults with VLBW by performing detailed oral glucose tolerance test (OGTT), which is useful for evaluation of early signs of glucose intolerance.

## METHODS

### Study participants

The birth record database of Seirei Hamamatsu General Hospital (Hamamatsu, Japan) showed that 628 subjects were born with VLBW between 1980 and 1990 and were treated at a neonatal intensive care unit (figure 1). VLBW infants were defined according to WHO criteria: babies whose birth weight was <1500 g. Out of the 628 subjects, 229 were excluded because of death (n=132) or severe neurodevelopmental impairment (n=97). To the remaining 399 subjects, we sent letters that provided information regarding the study and requested their participation. Among the 399 letters, 98 were returned marked as address unknown (ie, the remaining 301 letters were thought to reach their destinations). Consequently, 111 subjects (aged 19–30 years) participated in the present study. All participants were Japanese. Small for gestational age (SGA) status was determined according to standards by a study group of the Health Ministry in Japan: a birth weight below the 10th percentile for gestational age.[10] The basal characteristics of participants at birth are summarised in table 1.

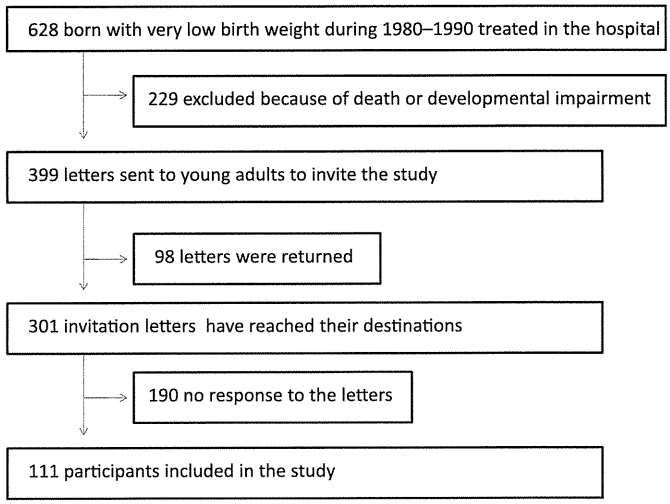


**Figure 1** Flow of participants through the study.

### Measurements

All participants underwent a standard 75 g OGTT after a 10 h overnight fast. Plasma glucose and serum insulin concentrations were examined at 0, 30, 60, 90, 120 and 180 min during OGTT. Fasting glucose levels and 2 h glucose levels were used for diagnosing diabetes mellitus, impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) according to WHO criteria.[11] Since it has been shown that 1 h plasma glucose concentration is associated with future risk of type 2 diabetes and atherosclerosis, 1 h plasma glucose above 8.6 mmol/l (155 mg/dl) was included as a category of hyperglycaemia.[12 13] Reactive hypoglycaemias during OGTT was defined as the level of plasma glucose <3.8 mmol/l, which causes the response of counter-regulatory hormone release.[14]

We measured plasma glucose and serum insulin levels during OGTT with an autoanalyzer JCA-BM2250 (JEOL, Tokyo, Japan). Plasma glucose was measured by means of hexokinase method. The concentration of serum insulin was measured with chemiluminescent enzyme immunoassay. Fasting blood samples were also drawn for other measurements, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride and creatinine. Glycated haemoglobin A1c (HbA1c) was measured with high-performance liquid chromatography method using an automated glycohaemoglobin analyser HLC-723G8 (Tosoh Bioscience, Tokyo, Japan). The values for HbA1c were converted from the Japanese Diabetes Society (JDS) values into the National Glycohaemoglobin Standardization Program (NGSP) equivalent values. The NGSP equivalent values were calculated with the formula: HbA1c (%) = JDS value (%)+0.4.[15]

### Calculations and statistical analysis

Pancreatic β cell function was evaluated by both insulinogenic index and homeostasis model of assessment for beta cell (HOMA-β).[16] Insulinogenic index, the index of early-phase insulin secretion, was calculated as the ratio

**Table 1** Clinical characteristics of young adults with very low birth weight at birth and at study assessment

| | | Men (n=42) | | Women (n=69) | |
|---|---|---|---|---|---|
| | Total (n=111) | SGA* (n=14) | AGA (n=28) | SGA* (n=25) | AGA (n=44) |
| At birth | | | | | |
| Gestational age (wk) | 29.7 (3.1) | 31.5 (3.7) | 28.1 (1.9) | 33.0 (2.6) | 28.2 (1.9) |
| Weight (g) | 1152 (235) | 1050 (223) | 1149 (235) | 1190 (239) | 1166 (236) |
| ELBW | 33 (29.7) | 6 (42.9) | 10 (35.7) | 7 (28.0) | 10 (22.7) |
| Birth from multiple pregnancy | 18 (16.2) | 2 (14.3) | 7 (25.0) | 1 (4.0) | 8 (18.2) |
| At study assessment | | | | | |
| Age (yr) | 24.8 (3.0) | 24.9 (2.9) | 24.6 (3.6) | 23.9 (2.9) | 25.4 (2.7) |
| Family history of diabetes | 22 (19.8) | 2 (14.3) | 5 (17.9) | 7 (28.0) | 8 (18.2) |
| Height (m) | 1.58 (0.07) | 1.60 (0.06) | 1.66 (0.06) | 1.54 (0.06) | 1.55 (0.05) |
| Body weight (kg) | 52.3 (10.1) | 53.1 (8.8) | 55.8 (8.9) | 47.5 (8.3) | 52.4 (11.3) |
| BMI (kg/m$^2$) | 20.9 (3.8) | 20.8 (3.2) | 20.3 (2.8) | 20.1 (3.0) | 21.7 (4.7) |
| Blood pressure (mm Hg) | | | | | |
| Systolic | 118 (16) | 120 (18) | 121 (17) | 115 (12) | 117 (16) |
| Diastolic | 70 (11) | 69 (15) | 69 (11) | 69 (11) | 71 (11) |
| Cholesterol (mg/dl) | | | | | |
| Total | 184.8 (31.3) | 210.6 (52.0) | 183.4 (25.2) | 180.4 (27.2) | 179.9 (25.1) |
| LDL | 104.3 (28.4) | 126.9 (48.6) | 104.8 (24.8) | 100.3 (21.5) | 99.0 (22.6) |
| HDL | 65.7 (13.3) | 63.2 (14.0) | 64.6 (14.1) | 64.6 (15.1) | 67.8 (11.6) |
| Triglycerides (mg/dl) | 81.8 (72.2) | 126.5 (139.9) | 81.0 (84.5) | 85.4 (51.0) | 65.9 (23.5) |
| Renal function | | | | | |
| Creatinine (mg/dl) | 0.66 (0.13) | 0.76 (0.09) | 0.80 (0.11) | 0.59 (0.08) | 0.58 (0.08) |
| eGFR (ml/min/1.73 m$^2$)† | 104.6 (18.4) | 105.5 (13.9) | 101.8 (19.4) | 104.3 (18.2) | 106.3 (19.5) |

*Determined by a birth weight below the 10th percentile for gestational age according to standards defined by a study group of the Health Ministry in Japan.
†Calculated according to the formula recommended by the Japanese Society of Nephrology: eGFR (ml/min/1.73 m$^2$)=194 × [Cre (mg/dl)]$^{-1.094}$ × [Age (years)]$^{-0.287}$ (×0.739 if the subject is a woman).
AGA, appropriate for gestational age; BMI, body mass index; eGFR, estimated glomerular filtration rate; ELBW, extremely low birth weight (<1000 g); HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGA, small for gestational age.
Data are expressed as mean (SD) or number (%).

of the increment in insulin concentration to the increment in glucose concentration ([30 min insulin (μU/ml) − fasting insulin]/[30 min glucose (mg/dl) − fasting glucose]). HOMA-β was calculated as follows: 20 × fasting insulin (μU/ml)/[fasting glucose (mmol/l) − 3.5]. Insulin resistance was estimated by homeostasis model of assessment for insulin resistance (HOMA-IR): fasting insulin (μU/ml) × fasting glucose (mmol/l)/22.5.[16] The total amounts of glucose and insulin levels during OGTT were assessed by calculating areas under the curve (AUC) with trapezoid rules. The estimated glomerular filtration rate (eGFR) was calculated according to the following formula, as recommended by the Japanese Society of Nephrology: eGFR (ml/min/1.73 m$^2$)=194 × [Cre (mg/dl)]$^{-1.094}$ × [Age (years)]$^{-0.287}$ (×0.739 if the subject is a woman).[17]

Quantitative variables were expressed as mean and SD or 95% CI; categorical variables were presented as number and percentage. Differences between groups were compared using the Student t test, the Mann–Whitney U test, the Pearson's $\chi^2$ test or the repeated measures analysis of variance (ANOVA) as appropriate. The data on insulin levels during OGTT were logarithmically transformed before the repeated measures ANOVA. Logistic regression analysis, which included gender, family history of diabetes within the second degree, body mass index (BMI), gestational age, birth weight and SGA/AGA (appropriate for gestational age), was performed to estimate ORs for the category of hyperglycaemia. For the further investigation into glucose regulation, multiple linear regression analysis was conducted. Gender, family history of diabetes, BMI, gestational age, birth weight and SGA/AGA were included in the model. The data on HOMA-β, HOMA-IR, insulinogenic index and glucose$_{AUC}$ were logarithmically transformed before analysis to meet the assumptions of normality. A p value of <0.05 was defined as statistically significant. All analyses were conducted using SAS software V.9.2 (SAS Institute) and the statistical software R V.2.12.2 (http://www.r-project.org).

## RESULTS

The basic characteristics of participants at study assessment are shown in table 1. Of 111 young adults with VLBW, 21 subjects (19%) had hyperglycaemia: one had type 2 diabetes, six had IGT, one had IFG and 13 non-diabetes/IGT/IFG subjects had elevated 1 h glucose levels (>8.6 mmol/l). Hyperglycaemia was more frequent in men than in women (26.2% for men vs 14.5% for women). In the logistic regression analysis

adjusted for family history of diabetes within the second degree, BMI, gestational age, birth weight and SGA/AGA, male gender was a statistically significant independent factor associated with hyperglycaemia (OR 3.34, 95% CI 1.08 to 10.3, p=0.036). BMI at study assessment was also associated with hyperglycaemia (table 2).

### Gender difference

As male gender was a significant independent risk factor of hyperglycaemia, we evaluated the differences in glucose regulation between men and women in the sample group. Figure 2 shows the glucose and insulin response during OGTT in men and in women. Male subjects had significantly higher levels of glucose during OGTT than female subjects (p<0.001 by repeated measures ANOVA). In terms of insulin levels, male subjects had lower levels of insulin during OGTT than female subjects (p=0.005 by repeated measures ANOVA). $Glucose_{AUC}$ during OGTT tended to be higher in male subjects (table 3). As for the function of insulin secretion, insulinogenic index and HOMA-β were significantly lower in men than in women. $Insulin_{AUC}$ also showed a tendency to be lower in male subjects. Reactive hypoglycaemias during OGTT tended to be frequent in men. The differences in the mean values of HbA1c and HOMA-IR were not statistically significant. There were no significant gender differences in gestational age (p=0.145), birth weight (p=0.168), age at study assessment (p=0.845), BMI (p=0.879), the proportion of SGA (p=0.756) and that of family history of diabetes within the second degree (p=0.516). The variables for glucose metabolism in men and women are summarised in table 3.

We evaluated the associations between gender and the variables of glucose metabolism by multiple linear regression analysis. Adjustments were made for family history of diabetes within the second degree, BMI, gestational age, birth weight and SGA/AGA. In this analysis, male gender had inverse associations with HOMA-β (β −0.336, 95% CI −0.509 to −0.163, p<0.001) and insulinogenic index (β −0.195, 95% CI −0.344 to −0.047, p=0.01). $Glucose_{AUC}$ during OGTT tended to be positively associated with male gender (β 0.056, 95% CI −0.0047 to 0.116, p=0.071).

In male subjects, after an adjustment for family history of diabetes, BMI, gestational age and birth weight, the logistic regression analysis showed that SGA was a statistically significant independent factor associated with hyperglycaemia (OR 33.3, 95% CI 1.67 to 662.6, p=0.022).

## DISCUSSION

To the best of our knowledge, this is the first study assessing the glucose regulation in young adults with VLBW in an Asian population. Our study has indicated that 19% of young adults with VLBW already had hyperglycaemia: type 2 diabetes, IGT, IFG and non-diabetes/IGT/IFG with high 1 h plasma glucose level. A report from the Japanese Ministry of Health, Welfare, and Labour in 2007 showed that of 204 general young adults (aged 20–29 years), two individuals (0.98%) had high levels of HbA1c (>6.0%; NGSP equivalent values),[18] while 3.6% of young adults with VLBW had the HbA1c values >6.0% in the present study. In a previous study, Hovi *et al*[9] reported that VLBW infants in young adulthood had higher indexes of glucose intolerance compared with term infants. A recent epidemiological study has also shown that preterm birth is associated with an increased risk of diabetes in young adults.[8] On the other hand, a study in the Netherlands showed that preterm birth was not associated with reduced insulin sensitivity in young adulthood.[19] The findings of that study may be biased by the way of recruiting the control subjects born at term. Our findings would be in line with the standpoint of high prevalence of hyperglycaemia in premature infants in young adulthood, although absence of control subjects presents a limitation of demonstrating the impact of VLBW itself on glucose regulation.

We have also found that male subjects had higher glucose levels during OGTT than females. Previous studies in the general population showed that women had higher postload glucose levels than men, which were explained by differences in body size.[20 21] During

**Table 2** Correlated factors for hyperglycaemia* in young adults with very low birth weight assessed by logistic regression analyses

| Variable | OR† (95% CI) | p Value |
|---|---|---|
| Gender (male) | 3.34 (1.08 to 10.3) | 0.036 |
| Factors at birth | | |
| Gestational age (wk) | 0.77 (0.53 to 1.12) | 0.165 |
| Weight (0.1 kg) | 1.39 (0.96 to 2.02) | 0.085 |
| SGA | 2.56 (0.37 to 17.5) | 0.340 |
| Factors at study assessment | | |
| Family history of diabetes | 1.92 (0.49 to 7.57) | 0.353 |
| BMI ($kg/m^2$) | 1.29 (1.11 to 1.49) | 0.001 |

*A category of hyperglycaemia includes diabetes, impaired glucose tolerance (IGT), impaired fasting glycaemia (IFG) and non-diabetes/IGT/IFG with elevated 1 h glucose levels (>8.6 mmol/l).
†Each OR is calculated from a model including gender, family history of diabetes, BMI, gestational age, birth weight and SGA/AGA (appropriate for gestational age).
BMI, body mass index; SGA, small for gestational age.

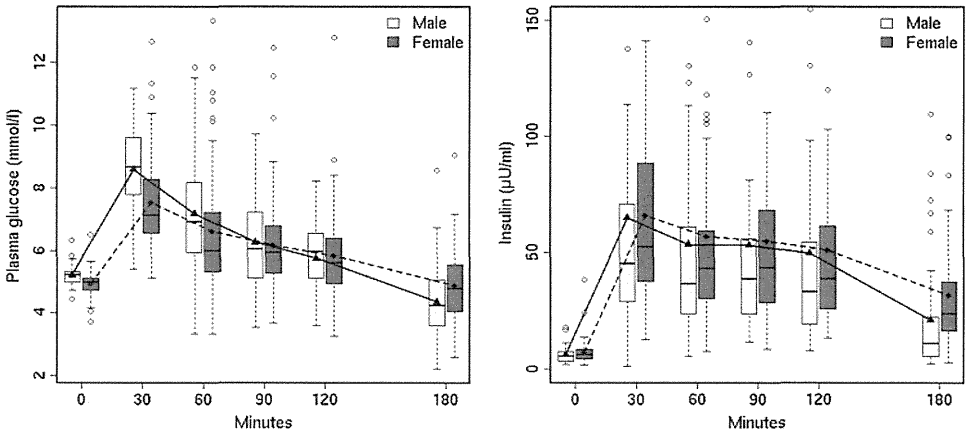


**Figure 2** The gender differences of glucose and insulin levels during oral glucose tolerance test (OGTT) in young adults with very low birth weight. The top and bottom of the box indicate lower and upper quartiles; the line inside the box represents the median; the whiskers indicate the most extreme data points within 1.5 times of IQR from the box; dots indicate outliers. Male subjects had significantly higher levels of glucose and lower levels of insulin during OGTT than female subjects ($p<0.001$ for glucose and $p=0.005$ for insulin by repeated measures analysis of variance).

standard 75 g OGTT, men and women take the same amount of glucose, which is thought to be high dosage for women relative to their body size. In our study, however, men had significantly higher levels of both fasting and postload glucose concentrations during OGTT. Moreover, male gender was associated with lower β cell function and the risk of glucose intolerance. These findings might indicate that men with VLBW are more predisposed to diabetes than women; indeed, recent studies have shown that male premature infants are more vulnerable than females.[22–27] In particular, the male sex is associated with various adverse outcomes including death,[25 27] respiratory dysfunction,[22] intraventricular haemorrhage,[24] autism spectrum[23] and neurodevelopmental impairment.[26] Interestingly, in the present study, the mean value of height (155 cm) in women with VLBW is close to the average value of the Japanese female population (158 cm), whereas men with VLBW (164 cm) were found to be shorter compared with the Japanese male population (171 cm) (average height data of Japanese population were drawn from the report by the Ministry of Education, Culture, Sports, Science, and Technology in Japan).[28] In a previous study, young adults who had been born SGA were shorter and had higher glucose levels than those with a normal birth weight.[29] Reduced final height might be long-term consequences of intrauterine retardation, which would also influence glucose regulation. Further investigation is needed to clarify whether the influence of VLBW on physical growth is more remarkable in male than in female infants and elucidate the relationship between physical growth and glucose regulation.

Previous studies have shown that SGA itself is associated with glucose intolerance.[30] In our study, SGA was not significantly associated with hyperglycaemia in total subjects but was associated in male subjects. The influence of SGA on glucose regulation in young adults with VLBW might be stronger in males than in females. It is

**Table 3** Gender differences in glucose regulation in young adults with very low birth weight

| | Men (n=42) | Women (n=69) | p Value |
|---|---|---|---|
| Hyperglycaemia | 11 (26.2) | 10 (14.5) | 0.127 |
| Diabetes | 0 | 1 | |
| IGT | 2 | 4 | |
| IFG | 1 | 0 | |
| Non-diabetes/IGT/IFG with elevated 1 h glucose levels* | 8 | 5 | |
| HbA1c (%) | 5.39 (5.31 to 5.47) | 5.39 (5.31 to 5.47) | 0.635 |
| HOMA-β | 72.5 (59.0 to 86.0) | 103 (87.2 to 119.6) | 0.001 |
| HOMA-IR | 1.4 (1.14 to 1.69) | 1.6 (1.29 to 1.90) | 0.477 |
| Variable during OGTT | | | |
| Insulinogenic index | 1.1 (0.64 to 1.60) | 1.4 (1.18 to 1.71) | 0.002 |
| $Glucose_{AUC}$ (mmol/l × h) | 18.8 (17.9 to 19.7) | 18.2 (17.3 to 19.0) | 0.089 |
| $Insulin_{AUC}$ (μU/ml × h) | 135.3 (98.7 to 171.9) | 145.1 (121.7 to 168.6) | 0.052 |
| Reactive hypoglycaemia | 17 (40) | 17 (25) | 0.079 |

*Defined as 1 h glucose levels >8.6 mmol/l.
HbA1c, haemoglobin A1c; HOMA-IR, homeostasis model of assessment for insulin resistance; HOMA-β, homeostasis model of assessment for beta cell; IFG, impaired fasting glycaemia; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.
Data are expressed as mean (95% CI) or n (%).

possible that this gender difference in glucose regulation is owing to the gender difference in the strength of SGA effect.

### Strength and weakness of the study

The major strength of our study is a well-characterised cohort of subjects with VLBW, who are quite rare in the general population (approximately 0.5% in this generation).[31] Our study includes a relatively large number of young adults with VLBW, and the individuals with profound complications were carefully excluded in the recruiting process. In addition, as participants in the cohort were all Japanese, their racial homogeneity made considerations of ethnic differences in glucose regulation unnecessary. To date, the glucose regulation of Asian young adults with VLBW has been uncertain. Our findings would be useful to clinicians and researchers and stimulate future large-scale prospective cohort studies in Asian populations.

In the present study, we could not obtain information regarding the growth rate in childhood of all participants. This is a major limitation of the study. The postnatal growth pattern in infancy has been shown to be associated with later glucose intolerance.[32–35] The clinical records of participants were written 20–30 years ago, and some of them were no longer preserved. Additionally, maternal factors such as advanced age, smoking, gestational diabetes, and perinatal complications were not available in the present study. These factors might have affected fetal malnutrition and subsequently led to VLBW. In terms of subjects in the present study, our study has no control subjects, presenting a limitation of demonstrating the impact of VLBW itself on glucose regulation. Another concern of the study is selection bias. Of 301 VLBW subjects who were thought to receive the invitation letters, 111 subjects (37%) participated in the study. The findings should be carefully interpreted taking into account the possibility that the participants might not be representative of general young adults with VLBW.

### Future perspective

As neonatal intensive care is making steady progress, an increasing number of young adults with VLBW worldwide will face a greater variety of health problems. Clinician should be aware of the risk of hyperglycaemia in young adults with VLBW and follow-up them for a longer period of time. It may be worthwhile for them to check their glucose metabolism with OGTT in their 20s or 30s, which would lead to early intervention in their lifestyle and subsequently contribute to prevention of type 2 diabetes and cardiovascular disease.[5–7] In the present study, we have found that male gender was a significant independent risk factor of hyperglycaemia in young adults with VLBW. In addition to the gender difference, future studies are required to focus on the factors affecting the glucose metabolism in VLBW infants.

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**Contributors** RS and HW drafted the paper. RS conceived the study. RS and KS developed the idea. RS, HW, KS, SO, RG, MM and HN were involved in study design. RS and KS participated in data acquisition. RS, HW, HM, EI, MT and MM were engaged in data analysis. All the authors contributed to the interpretation of the findings. All the authors were involved in the revision and approved the final version.

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**Competing interests** None.

**Ethical approval** The study was approved by the ethical committee of Seirei Hamamatsu General Hospital. All participants provided written informed consent to participate in the study.

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**Data sharing statement** Data will not be publically accessible. However, interested individuals may contact the authors.

## REFERENCES

1. Field DJ, Dorling JS, Manktelow BN, *et al.* Survival of extremely premature babies in a geographically defined population: prospective cohort study of 1994-9 compared with 2000-5. *BMJ* 2008;336:1221–3.
2. Barker DJ, Gluckman PD, Godfrey KM, *et al.* Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993;341:938–41.
3. Kaijser M, Bonamy AK, Akre O, *et al.* Perinatal risk factors for diabetes in later life. *Diabetes* 2009;58:523–6.
4. Whincup PH, Kaye SJ, Owen CG, *et al.* Birth weight and risk of type 2 diabetes: a systematic review. *JAMA* 2008;300:2886–97.
5. Knowler WC, Barrett-Connor E, Fowler SE, *et al.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
6. Eriksson KF, Lindgarde F. Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise. The 6-year Malmo feasibility study. *Diabetologia* 1991;34:891–8.
7. Tuomilehto J, Lindstrom J, Eriksson JG, *et al.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 2001;344:1343–50.
8. Crump C, Winkleby MA, Sundquist K, *et al.* Risk of diabetes among young adults born preterm in Sweden. *Diabetes Care* 2011;34:1109–13.
9. Hovi P, Andersson S, Eriksson JG, *et al.* Glucose regulation in young adults with very low birth weight. *N Engl J Med* 2007;356:2053–63.
10. The study group of the Health Ministry in Japan. *Fetal Growth Curves of Japanese.* Tokyo: The Ministry of Health, Labour, and Welfare, 1994:61.
11. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications.* Geneva: World Health Organization, 1999.

12. Abdul-Ghani MA, Abdul-Ghani T, Ali N, *et al.* One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. *Diabetes Care* 2008;31:1650–5.
13. Succurro E, Marini MA, Arturi F, *et al.* Elevated one-hour post-load plasma glucose levels identifies subjects with normal glucose tolerance but early carotid atherosclerosis. *Atherosclerosis* 2009;207:245–9.
14. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care* 2005;28:2948–61.
15. The Committee of Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. *J Japan Diab Soc* 2010;53:450–67.
16. Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–19.
17. Matsuo S, Imai E, Horio M, *et al.* Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009;53:982–92.
18. The Ministry of Health, Labour, and Welfare. *The National Health and Nutrition Survey in Japan*. Tokyo: Daiichi-shuppan Publishing Company, 2007:187.
19. Willemsen RH, Leunissen RW, Stijnen T, *et al.* Prematurity is not associated with reduced insulin sensitivity in adulthood. *J Clin Endocrinol Metab* 2009;94:1695–700.
20. Faerch K, Borch-Johnsen K, Vaag A, *et al.* Sex differences in glucose levels: a consequence of physiology or methodological convenience? The Inter99 study. *Diabetologia* 2010;53:858–65.
21. Sicree RA, Zimmet PZ, Dunstan DW, *et al.* Differences in height explain gender differences in the response to the oral glucose tolerance test- the AusDiab study. *Diabet Med* 2008;25:296–302.
22. Henderson-Smart DJ, Hutchinson JL, Donoghue DA, *et al.* Prenatal predictors of chronic lung disease in very preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006;91:F40–5.
23. Johnson S, Hollis C, Kochhar P, *et al.* Autism spectrum disorders in extremely preterm children. *J Pediatr* 2010;156:525–31.e2.
24. Mohamed MA, Aly H. Male gender is associated with intraventricular hemorrhage. *Pediatrics* 2010;125:e333–9.
25. Morse SB, Wu SS, Ma C, *et al.* Racial and gender differences in the viability of extremely low birth weight infants: a population-based study. *Pediatrics* 2006;117:e106–12.
26. Spinillo A, Montanari L, Gardella B, *et al.* Infant sex, obstetric risk factors, and 2-year neurodevelopmental outcome among preterm infants. *Dev Med Child Neurol* 2009;51:518–25.
27. Tyson JE, Parikh NA, Langer J, *et al.* Intensive care for extreme prematurity—moving beyond gestational age. *N Engl J Med* 2008;358:1672–81.
28. The Ministry of Education, Culture, Sports, Science, and Technology in Japan. *A Report of School Health Statistics*. Tokyo: National Printing Bureau, 2004.
29. Leger J, Levy-Marchal C, Bloch J, *et al.* Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study. *BMJ* 1997;315:341–7.
30. Saenger P, Czernichow P, Hughes I, *et al.* Small for gestational age: short stature and beyond. *Endocr Rev* 2007;28:219–51.
31. Vital Statistics. *The Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour, and Welfare*. Vol. 1. Japan: Vital Statistics, 2009:124–7.
32. Crowther NJ, Cameron N, Trusler J, *et al.* Influence of catch-up growth on glucose tolerance and beta-cell function in 7-year-old children: results from the birth to twenty study. *Pediatrics* 2008;121: e1715–22.
33. Eriksson JG, Osmond C, Kajantie E, *et al.* Patterns of growth among children who later develop type 2 diabetes or its risk factors. *Diabetologia* 2006;49:2853–8.
34. Finken MJ, Keijzer-Veen MG, Dekker FW, *et al.* Preterm birth and later insulin resistance: effects of birth weight and postnatal growth in a population based longitudinal study from birth into adult life. *Diabetologia* 2006;49:478–85.
35. Leunissen RW, Kerkhof GF, Stijnen T, *et al.* Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood. *JAMA* 2009;301:2234–42.

# A cross-sectional study of glucose regulation in young adults with very low birth weight: impact of male gender on hyperglycaemia

Ryosuke Sato, Hiroshi Watanabe, Kenji Shirai, et al.

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**Notes**

# Cancer Risk in Diabetic Patients Treated with Metformin: A Systematic Review and Meta-analysis

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## Abstract

*Background:* A growing body of evidence has suggested that metformin potentially reduces the risk of cancer. Our objective was to enhance the precision of estimates of the effect of metformin on the risk of any-site and site-specific cancers in patients with diabetes.

*Methods/Principal Findings:* We performed a search of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov for pertinent articles published as of October 12, 2011, and included them in a systematic review and meta-analysis. We calculated pooled risk ratios (RRs) for overall cancer mortality and cancer incidence. Of the 21,195 diabetic patients reported in 6 studies (4 cohort studies, 2 RCTs), 991 (4.5%) cases of death from cancer were reported. A total of 11,117 (5.3%) cases of incident cancer at any site were reported among 210,892 patients in 10 studies (2 RCTs, 6 cohort studies, 2 case-control studies). The risks of cancer among metformin users were significantly lower than those among non-metformin users: the pooled RRs (95% confidence interval) were 0.66 (0.49–0.88) for cancer mortality, 0.67 (0.53–0.85) for all-cancer incidence, 0.68 (0.53–0.88) for colorectal cancer (n = 6), 0.20 (0.07–0.59) for hepatocellular cancer (n = 4), 0.67 (0.45–0.99) for lung cancer (n = 3).

*Conclusion/Significance:* The use of metformin in diabetic patients was associated with significantly lower risks of cancer mortality and incidence. However, this analysis is mainly based on observational studies and our findings underscore the more need for long-term RCTs to confirm this potential benefit for individuals with diabetes.

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## Introduction

Hyperinsulinemia and hyperglycemia are thought to promote carcinogenesis in patients with diabetes mellitus. Several meta-analyses have demonstrated that diabetes is associated with increased risks of site-specific cancers of the breast (1.2) [1], endometrium (2.1) [2], bladder (1.2) [3], liver (2.5) [4], colorectum (1.3) [5], and pancreas (1.8–2.1) [6,7], and also a decreased risk of prostate cancer (0.8–0.9) [8,9]. The evidence for non-Hodgkin's lymphoma remains inconclusive [10,11]. Our previous meta-analyses showed that patients with diabetes have an increased risk of total cancer (relative risk, 1.1–1.7) [12–14], whereas more recent studies did not [15,16]. Metformin is an insulin sensitizer that is the drug of first choice in the management of type 2 diabetes [17], given its safety profile and lower cost. Metformin reportedly has a potential anti-cancer effect by activating adenosine 5′-mono-phosphate-activated protein kinase (AMPK) in addition to alleviating hyperinsulinemia and hyperglycemia. Although other mechanisms for this risk reduction have been hypothesized, none have been elucidated entirely. Previous meta-analyses have suggested that metformin is associated with a reduced risk of cancer in diabetic subjects [18,19]. However, those analyses were based solely on a few observational studies and additional reports have been published recently.

In light of the worldwide diabetes epidemic and the higher mortalities in cancer patients with diabetes [20,21], explorations of effective cancer prevention are of clinical importance for the targeted management of diabetes in daily practice. Moreover, they are crucial in the areas of public health, since a modest increase in the risk of cancer translates into a substantial social burden. These circumstances prompted us to investigate, with greater precision, the preventive effect of metformin on cancer mortality and incidence by scrutinizing pertinent original reports including randomized controlled trials (RCTs), and combining their data in an attempt to obtain meaningful clues for the prevention of cancer in patients with diabetes [13].

## Methods

### Search

Searches of MEDLINE, EMBASE, ISI Web of Science, Cochrane Library, and ClinicalTrials.gov from their inception until October 12, 2011, were performed. Studies evaluating the risks of cancer mortality or incidence among diabetic patients

taking metformin, compared with those not taking metformin, were identified using a combination of the following medical subject heading terms: 'diabetes', 'metformin', 'cancer' or 'neoplasms', and 'risk' or 'risk factors'. The reference lists of the pertinent articles were also inspected.

### Selection/Study Characteristics

We assessed all the identified RCTs, cohort studies, case-control studies, and cross-sectional studies on the risk of cancer based on original data analyses to determine their eligibility for inclusion in a qualitative analysis. The inclusion criteria in the meta-analysis are as follows: published full-text report in English-language, RCTs with parallel-design of metformin as a treatment of type 2 diabetes at least one year's follow-up period, observational studies of any duration in patients with type 2 diabetes, reporting relative risks, i.e. hazard ratios (HRs), RRs, or odds ratios, adjusted for possible confounders with confidence intervals (CIs). The comparators were defined as any treatment not including metformin.

### Validity assessment

To ascertain the validity of the eligible studies, the quality of each report was appraised in reference to the CONSORT statement [22] and the STROBE statement [23].

### Data abstraction

We reviewed each full-text report to determine its eligibility and extracted and tabulated all the relevant data independently. The extracted data included the characteristics of the subjects (including age, sex, and other treatment), study design, published year, follow-up period, and the methods used for ascertaining the diagnosis of cancer. Study authors were contacted as needed to obtain detailed data. Any disagreement was resolved by a consensus among the investigators.

### Quantitative data synthesis

If more than one study was published for the same cohort, the report containing the most comprehensive information on the population was included to avoid overlapping populations. The reports were summarized both qualitatively and quantitatively. Three articles that did not specify the case numbers were not included in the calculation of the mortality and incidence. If the metformin comparator included more than one treatment, the oral monotherapy groups were included in the analysis because these groups were deemed to be at an equivalent stage of diabetes. If an article provided the relative risks for all cancer and site-specific cancers, the all cancer data were included in the primary qualitative and quantitative analyses and the site-specific data were used in the secondary analyses performed according to cancer site. The risks for site-specific cancers were appraised if three or more qualified reports were identified for a given cancer site. Response to metformin exposure was evaluated by using linear-regression analysis.

In the meta-analysis, each adjusted relative risk was combined and the pooled RRs with the 95% CI was calculated using the random-effects model with inverse-variance weighting. Heterogeneity among the studies was evaluated using $I^2$ statistics. The possibility of a publication bias, which can result from the non-publication of small studies with negative findings, was assessed visually using a funnel plot for asymmetry. RevMan (version 5.1) was used for these calculations. A sensitivity analysis was performed by separating the RCTs and the observational cohort / case-control studies and the equality of RRs between RCTs and observational studies were assessed by using $z$-statistic tests. All the procedures were in accordance with the guidelines for the Quality of Reporting of Meta-analyses [24], the meta-analysis of observational studies in epidemiology [25] and the PRISMA statement [26].

## Results

### Search Results

A total of 412 articles were identified during our search; of these, 32 were assessed with respect to their eligibility for inclusion in our review, which was aimed at determining the influence of metformin on cancer mortality and incidence in patients with diabetes (**Fig. 1**). Four articles [27–30] were excluded from the systematic review because of population overlapping and four other reports were excluded because they investigated the overall survival rate [31,32], cancer incidence exclusively in patients with hepatitis C [33], and biochemical recurrence [34]. Out of these 32 articles, a total of 24 (11 observational cohort studies [35–45], 3 randomized controlled trials [46–49], and 10 case-control studies [29,50–58]) were included in the systematic review and meta-analysis. The UK Prospective Diabetes Study (UKPDS) 34 [49] involved two independent investigational trials (metformin vs. conventional therapy and sulfonylurea vs. sulfonylurea plus metformin), and these trials were included in the meta-analysis as two separate data.

**Table S1** shows the characteristics of each included study according to the study design. The 24 selected articles included in the systematic review were moderately heterogeneous in terms of population demographics, study design, and the assessment of confounding factors. The diabetes sample size in these studies ranged from 361 to 998,947 patients. Of the 21,195 diabetic patients in 6 studies, 991 (4.5%) cases of cancer death were reported. A total of 11,117 (5.3%) cases of incident cancer at any site were reported among 210,892 patients in 10 studies. Major confounding factors such as cigarette smoking, alcohol intake, and hyperglycemia were not reported in several studies.

The risk of bias and the adjustment factors among the studies are summarized in **Table S2.** Diabetes was diagnosed using blood tests (n = 8), prescription databases (n = 6), medical records (n = 4), self-reports (n = 3), and health insurance database (n = 4). All the diagnoses of cancer were confirmed using valid records or registries. All the studies, except for the RCTs, adjusted the estimates for potential confounding factors. The analysis of dose-response was performed in 3 studies [38–40]. Some studies excluded the data for metformin exposure less than 1 year [50,52] or 2 years [58] to minimize bias. The effect on the total cancer risk over the follow-up period was inspected in 3 studies [40,55,58]. Direct comparison of the effect between metformin and other specific medications were reported in 2 RCTs [46–48].

### Qualitative Summary

The majority of the studies included were methodologically fair in quality. Among 10 case-control studies, six were nested ones [50–52,55,56,58]. All the four cohort studies [35,38,40,41] on cancer mortality revealed a significant decrease (range, 23%–75%), and the two RCTs showed no significant effect of metformin [49]. There was no study that directly compared the risk associated with metformin vs other medications or analyzed the correlation between the follow-up length and the effect of metformin on cancer mortality. The overall correlation of the follow-up period with the mortality was nonsignificant ($r = -0.04$, $p = 0.9$). One study revealed that the HR (95% CI) for cancer mortality with every increase of 1 g metformin was 0.58 (0.36–0.93) [38].

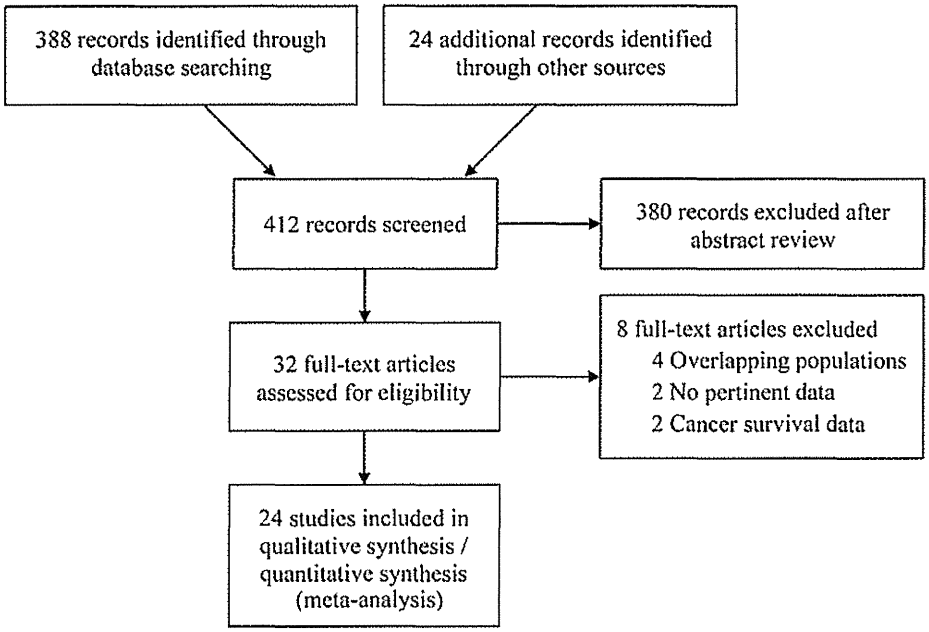


**Figure 1. Flow diagram of study selection.**
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Five studies (3 cohort studies [36,39,40] and 2 case-control studies [55,56]) reported a significant decrease (range, 26%–88%), the two RCTs showed no significant effect of association [46–48] and none demonstrated a statistically significant increase in the risk of all-cancer incidence among metformin users. The cancer risk for metformin users was not significantly different from that for rosiglitazone or sulfonylurea users in RCTs [46–48]. One cohort study showed a trend for metformin users to have a higher risk of cancer in the first 2 years of follow-up. The beneficial effect of metformin on the risk of total cancer incidence was exposure-dependent in 2 case-control studies [55,56]. The overall correlation of the follow-up period with the incidence was nonsignificant ($r = -0.32$, $p = 0.4$). One study reported that its effect on cancer incidence was dose-dependent (p for trend $<0.05$) [39] suggesting that the minimal effective dose can be 500 mg /day, while the other showed no significant differences among doses [40].

Among the studies evaluating the risks of site-specific incident cancers in patients with diabetes who were taking metformin, more than two studies (including subgroup analyses) recognized significantly reduced risks for cancers of the pancreas [36,39,54], colorectum [36,39,40], and liver [29,39,53], and none showed a significantly increased risk of a site-specific cancer. All these risk decrements were moderate (RR range, 0.06–0.60). Of note, no significant increases or decreases in the risk of cancers of the breast, prostate or stomach were reported, except for a significant decrease in the risk of prostate cancer in one report [42] and breast cancer in another [52]. The number of studies examining other cancer sites was two or fewer, and these studies were not reviewed in the present analysis.

### Quantitative Summary (Meta-analysis)

Based on the quality appraisal in our systematic review, a total of 24 articles that provided sufficient information were included in the meta-analysis (**Fig. 1**). **Fig. 2** illustrates the significantly decreased risks of all-cancer mortality and incidence in metformin-users, compared with non-metformin users. In a sensitivity analysis, the pooled estimate (95% CI) for all-cancer mortality among the observational cohort studies was 0.62 (0.46–0.82), $I^2 = 56\%$, $p = 0.08$ and the estimate among the RCTs was 1.22 (0.36–4.11), $I^2 = 60\%$, $p = 0.12$. The difference in the RRs between the observational studies and the RCTs was not statistically significant ($p = 0.35$). The pooled RR (95% CI) for all-cancer incidence among the observational cohort studies was 0.66 (0.49-0.88), $I^2 = 96\%$, $p<0.00001$, the pooled RR among the case-control studies was 0.38 (0.23-0.61), $I^2 = 3\%$, $p = 0.31$ and the estimate among the RCTs was 1.03 (0.82–1.31), $I^2 = 30\%$, $p = 0.23$. The difference in the RRs between the observational studies and the RCTs was statistically significant ($p = 0.019$). As summarized in **Fig. 3 and Fig. 4**, the incident cancer risks were also significantly decreased for cancers of the colorectum, liver and lung. The RRs of prostate cancer, breast cancer, pancreatic cancer and gastric cancer were not statistically significant. Significant heterogeneity was observed in the majority of these analyses. No apparent publication bias was apparent, as assessed using a funnel plot (**Fig. S1**).

## Discussion

Our systematic review and meta-analyses of worldwide reports demonstrated that metformin is associated with a substantially lower risk of all-cancer mortality and incidence, compared with other treatments for diabetes. They also showed that metformin significantly reduced the risks of cancers of the colorectum, liver and lung. These findings support the hypothesis that metformin potentially has an anti-cancer effect. In light of the fact that cancer is the second and diabetes the twelfth leading cause of death worldwide [59] and that the number of people with diabetes is rapidly increasing, our findings have substantial clinical and public implications on a global scale and point to the need for the further investigation of the anti-cancer mechanism of metformin and for long-term RCTs to confirm this clinical benefit.

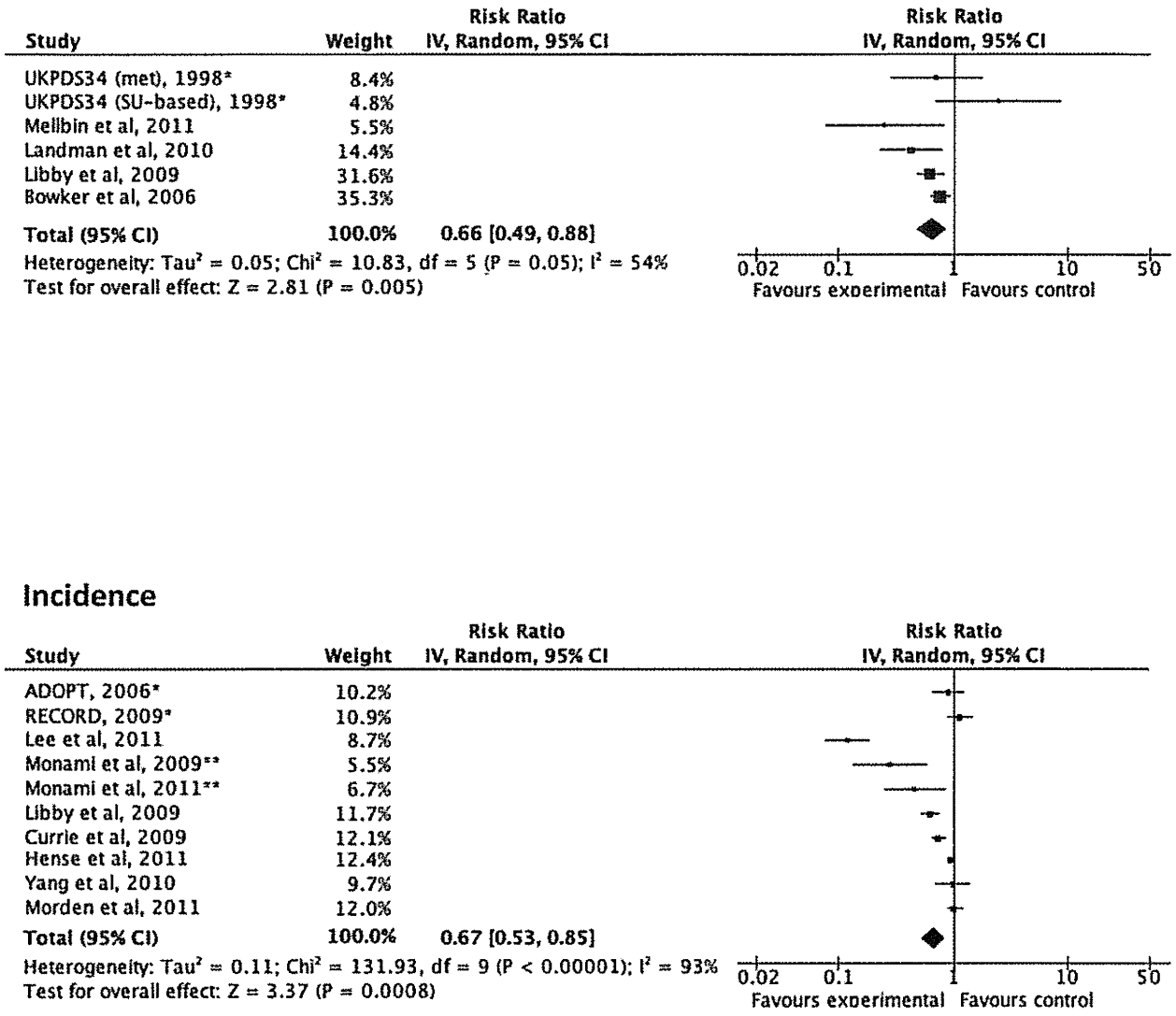


**Figure 2. Adjusted risk ratios for all-cancer mortality and incidence among subjects with diabetes taking metformin.** Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
doi:10.1371/journal.pone.0033411.g002

The strength of our present study is that the analysis was mainly based on large population-based data originating from multiple nations and was performed with a high level of precision. Compared with recently published studies [18,19], our updated study is novel in that data from RCTs were incorporated and cancer risks for substantially more sites were analyzed. Although the significantly decreased pooled RRs for all-cancer mortality / incidence and cancer at most sites were robust, the results of the component studies were statistically heterogeneous. Of note, all the individual and pooled results of the RCTs were neutral. It seems that each follow-up period in these RCTs is similar to many others in the observational studies and they have power enough to detect the differences in cancer risk. In the analysis of cancer mortality, there was no significant difference in RR between the RCTs and the observational studies. For cancer incidence, on the other hand, the overall RR was significantly reduced but the difference was statistically significant. This discordance may imply that the apparent anti-cancer effect of metformin in observational studies was affected by confounding biases and thus more RCTs are awaited to clarify the effect of metformin on cancer incidence. The large $I^2$ values indicated that the range of the plausible risk estimates was wide but no evidence in our analysis suggested that metformin may increase the risk of cancer. These findings may reflect the different mechanisms of cancer prevention at different sites and / or different epidemiological characteristics among the diverse populations included in our study.

Evidence has been accumulating to suggest that diabetic patients have a higher risk of cancer than non-diabetic people [12,13]. While the mechanisms are yet to be investigated, insulin resistance with secondary hyperinsulinemia is the most frequently proposed hypothesis, as insulin may have a possible mitogenic effect via its binding to the insulin-like growth factor-1 receptor

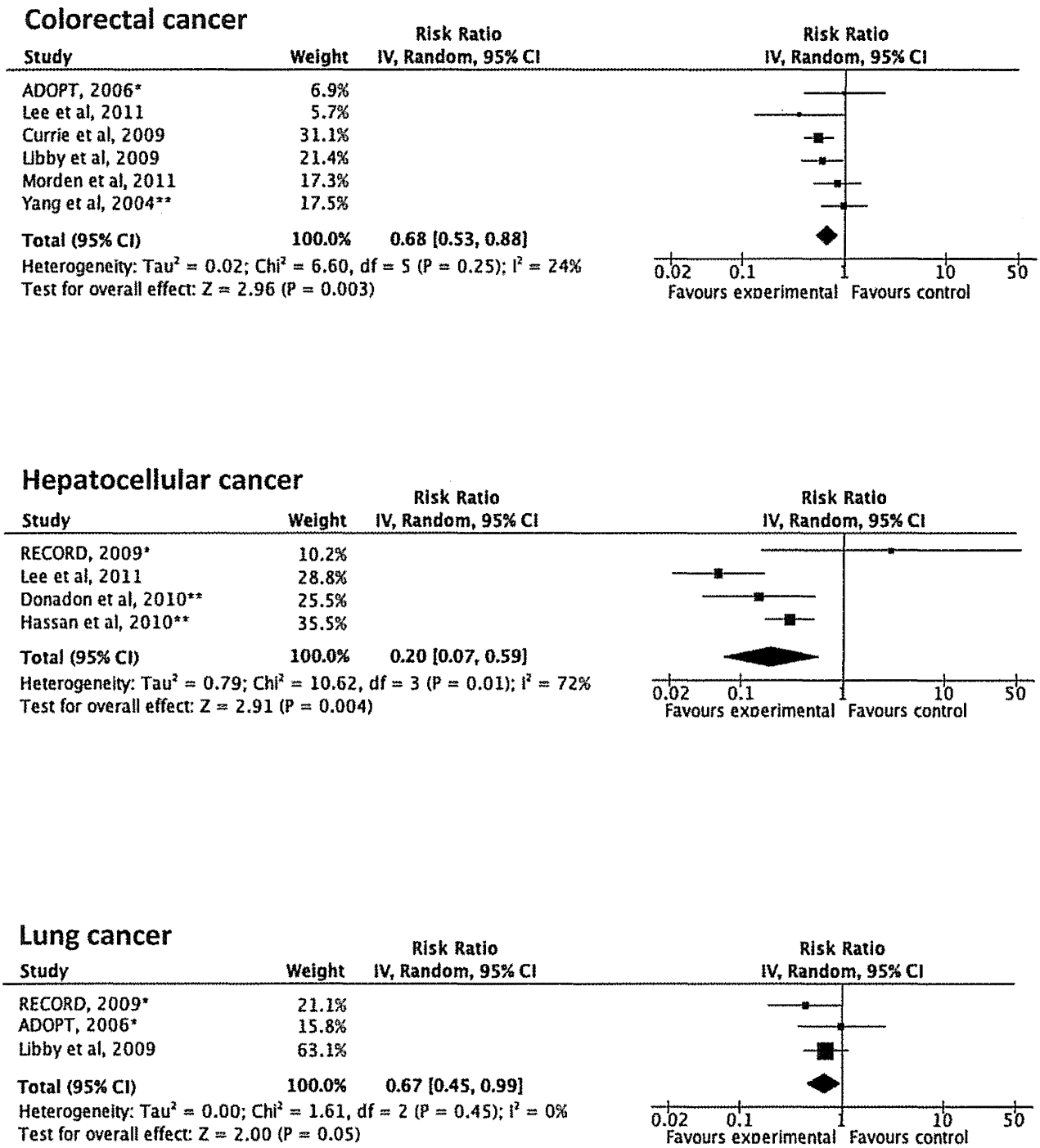


**Figure 3. Adjusted risk ratios for site-specific cancer incidence among subjects with diabetes taking metformin.** Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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[60–70]. In addition, hyperglycemia itself may promote carcinogenesis directly [71,72] or indirectly by increasing oxidative stress [73–79]. However, these speculations are derived from retrospective observational studies and may not necessarily demonstrate causality because of possible biases and confounders, such as co-existing obesity and age [15,80,81]. In fact, more recent studies demonstrated no or minimal increments in cancer risk [15,16] and the data from insulin-treated patients are inconclusive [82]. Of interest, diabetes reportedly protects against the development of prostate cancer [8,9], since it is testosterone-dependent and testosterone deficiency is common among men with diabetes secondary to low levels of sex hormone-binding globulin (SHBG)

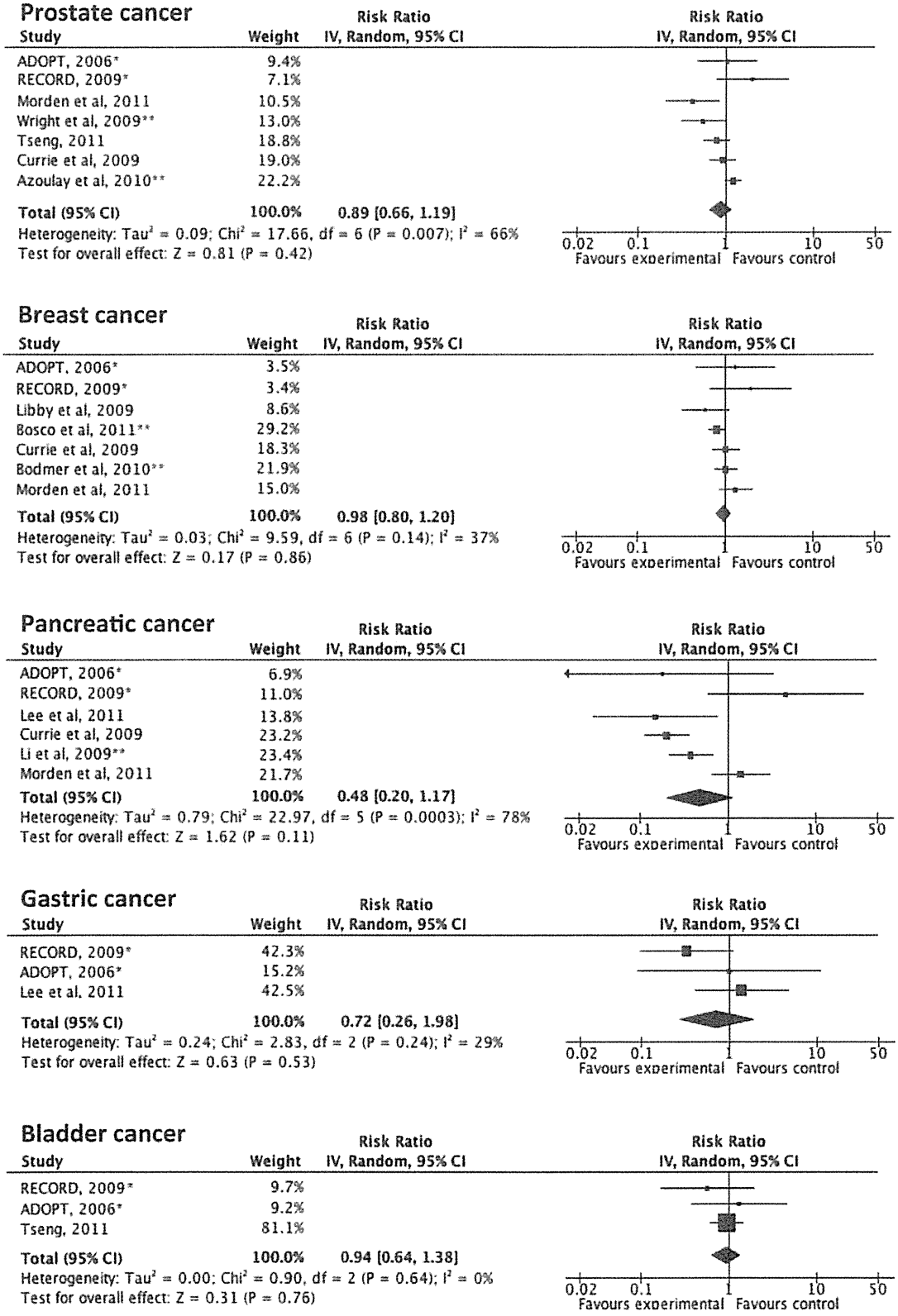


**Figure 4. Adjusted risk ratios for other site-specific cancer incidence among subjects with diabetes taking metformin.** Boxes, estimated risk ratios (RRs); bars, 95% confidence intervals (CIs). Diamonds, random-effects model RRs; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. *, randomized controlled trials; **, case-control studies; IV, inverse-variance.
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and partially because of insulin resistance [83–85]. Low SHBG levels may facilitate the conversion of testosterone to estradiol, which in turn may result in an increased risk of hormone-dependent breast cancer.

Several mechanisms for the anti-cancer effect of metformin have been postulated, and several prospective clinical trials to evaluate its safety and efficacy are ongoing [82,86]. Indirect pathways include the prevention of weight gain and the amelioration of hyperinsulinemia, both of which may promote carcinogenesis. In addition, metformin activates AMPK through LKB-1, a tumor suppressor protein kinase. AMPK inhibits protein synthesis and gluconeogenesis during cellular stress and inhibits mammalian target of rapamycin (mTOR), a downstream effector of growth factor signaling, which is frequently activated in malignant cells. In human breast cancer cells, it reduces HER-2 protein expression by inhibiting mTOR. Metformin also induces cell cycle arrest and apoptosis and reduces growth factor signaling. Supporting the idea of these direct effects, metformin reportedly potentiated the effect of neoadjuvant chemotherapy in early-stage breast cancer [87], decreased the risk of colorectal cancer in a small randomized trial involving non-diabetic subjects [88], and was associated with a decreased cancer risk while another insulin-sensitizer, thiazolidinedione, were not [18,54, 89,90].

Our research revealed that metformin use is associated with reduced mortality and incidence of cancer at any site, supporting the general applicability of the proposed anti-cancer mechanisms. The anti-cancer effect of metformin may also be applicable to diabetic Asians, who are generally lean and insulinopenic [12], given the fact that they have a higher cancer risk than non-diabetic Asians [12–14] and the data for Asians [39] were in line with the results of our meta-analyses. On the other hand, the magnitude of the risk reduction varies among site-specific cancers. This variance in efficacy may result from differences in carcinogenesis at certain sites. For instance, elevated levels of insulin and glucose may exert an important influence in the development or growth of epithelial malignant tumors of the colon [91–93], pancreas [94,95], and breast [96], and metformin may prevent incident colon cancer in non-diabetic subjects [88]. An animal study suggested that metformin prevented smoking-related lung cancer in mice, probably by inducing some hormone from the liver [97]. With regard to sex hormone-dependent cancers, the effect of metformin on the development of prostate cancer and breast cancer in our analysis was neutral. Metformin improves insulin sensitivity, thereby possibly raising the testosterone level. This may have promoted prostate cancer development and may have diluted the beneficial effect of metformin. In fact, one cohort study reported no benefit of metformin in terms of the biochemical recurrence rate after radical prostatectomy in diabetic patients [34]. The nonsignificant pooled RR for breast cancer may have resulted from the diversity in confounder adjustments and follow-up periods: some analyses were not fully adjusted for risk factors, including the menopause status, and one study suggested that only long-term exposure to metformin reduced the risk of breast cancer [51]. The fact that one preliminary study suggested a promising effect of metformin on pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer [87] may point to the possibility that metformin simply augmented the efficacy of chemotherapy for breast cancer [18,86]. Further detailed studies to analyze the interaction between carcinogenesis and the action of metformin, and to evaluate its effect for nondiabetic people are eagerly awaited.

### Limitations

Our analysis should be interpreted in the context of the following limitations. First, the relation may not necessarily be causal, particularly in the observational studies [80], because of possible confounding factors and biases that may not have been fully adjusted for in this study: some risk factors such as cigarette smoking, alcohol intake, and hyperglycemia were not specified in several studies, which may have rendered the results less valid. Few studies demonstrated the dose-response to support biological plausibility. Confounding by treatment indication [98], which may have been minimizes by using propensity-score matching analysis, might overestimate the effect of metformin: the presence of such pre-existing conditions as older age and liver disease precludes metformin usages and thus, metformin users may be generally younger and at lower risk of cancer than in those in comparator groups. Only a few observational studies analyzed the effects over time and thus protopathic bias (i.e. early cancer leading to unstable diabetes and hyperglycemia, with patients switching diabetes treatment) [15] may remain moderate. In fact, the individual and pooled estimates from the RCTs were all neutral; the estimates comparing with other medication were neutral, as well. For all these limitations, however, observational studies provide the good available evidence regarding potential treatment effects / harms and the overall pooled estimates were robust. Moreover, evidence has been accumulating to support causality, both clinically and biochemically, as discussed earlier. Secondly, it is also important to realize that the populations of the studies were heterogeneous, most likely because of the diversity of the study designs and ethnicities, and that the sensitivity of each site-specific cancer to metformin may vary. Lack of the standardized treatment protocol in the descriptive studies might explain the observed associations: the possibility that other diabetes treatments may increase the risk of cancer may have resulted in an overestimation of the effect of metformin. Lack of the standardized diagnostic procedures for cancer may have caused detection bias in some cases. Even with these limitations, our analysis supports oncogenic safety of metformin and it should provide physicians with an additional incentive to pay integrated clinical attention and elucidate the complex interactions between diabetes treatment and cancer.

### Conclusions

Our meta-analysis favors the oncogenic benefit of metformin for diabetic patients. However, observational studies were moderately heterogeneous and biased, and RCTs did not show a significant effect. Our findings underscore the need for long-term randomized prospective studies to confirm this potential benefit.

## Supporting Information

**Figure S1 Funnel plot of the included studies.**
(TIFF)

**Table S1 Study characteristics.**
(DOC)

**Table S2 Quality assessments of the included studies.**
(DOC)

**Checklist S1 PRISMA Checklist.**
(PDF)

## Author Contributions

Conceived and designed the experiments: HN MN. Performed the experiments: HN AG TT. Analyzed the data: HN AG TT. Contributed reagents/materials/analysis tools: HN AG TT. Wrote the paper: HN. Reviewed/edited the manuscript: AG TT MN.

## References


1. Larsson SC, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 121: 856–862.
2. Friberg E, Orsini N, Mantzoros CS, Wolk A (2007) Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 50: 1365–1374.
3. Larsson SC, Orsini N, Brismar K, Wolk A (2006) Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 49: 2819–2823.
4. El-Serag HB, Hampel H, Javadi F (2006) The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 4: 369–380.
5. Larsson SC, Orsini N, Wolk A (2005) Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst 97: 1679–1687.
6. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M (2005) Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 92: 2076–2083.
7. Everhart J, Wright D (1995) Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 273: 1605–1609.
8. Bonovas S, Filioussi K, Tsantes A (2004) Diabetes mellitus and risk of prostate cancer: a meta-analysis. Diabetologia 47: 1071–1078.
9. Kasper JS, Giovannucci E (2006) A meta-analysis of diabetes mellitus and the risk of prostate cancer. Cancer Epidemiol Biomarkers Prev 15: 2056–2062.
10. Mitri J, Castillo J, Pittas AG (2008) Diabetes and risk of Non-Hodgkin's lymphoma: a meta-analysis of observational studies. Diabetes Care 31: 2391–2397.
11. Chao C, Page JH (2008) Type 2 diabetes mellitus and risk of non-Hodgkin lymphoma: a systematic review and meta-analysis. Am J Epidemiol 168: 471–480.
12. Noto H, Osame K, Sasazuki T, Noda M (2010) Substantially increased risk of cancer in patients with diabetes mellitus: a systematic review and meta-analysis of epidemiologic evidence in Japan. J Diabetes Complications 24: 345–353.
13. Noto H, Tsujimoto T, Sasazuki T, Noda M (2011) Significantly Increased Risk of Cancer in Patients with Diabetes Mellitus. Endocrine Practice 17: 616–628.
14. Noto H, Tsujimoto T, Noda M (in press) Significantly Increased Risk of Cancer in Diabetes Mellitus Patients: A meta-analysis of epidemiologic evidence in Asians and non-Asians. Journal of Diabetes Investigation.
15. van Staa TP, Patel D, Gallagher AM, de Bruin ML (2011) Glucose-lowering agents and the patterns of risk for cancer: a study with the General Practice Research Database and secondary care data. DiabetologiaNov 30. [Epub ahead of print].
16. Wotton CJ, Yeates DG, Goldacre MJ (2011) Cancer in patients admitted to hospital with diabetes mellitus aged 30 years and over: record linkage studies. Diabetologia 54: 527–534.
17. Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, et al. (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32: 193–203.
18. Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, et al. (2010) Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila) 3: 1451–1461.
19. Zhang ZJ, Zheng ZJ, Kan H, Song Y, Cui W, et al. (2011) Reduced Risk of Colorectal Cancer With Metformin Therapy in Patients With Type 2 Diabetes: A meta-analysis. Diabetes Care 34: 2323–2328.
20. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, et al. (2008) Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 300: 2754–2764.
21. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, et al. (2010) Postoperative mortality in cancer patients with preexisting diabetes: systematic review and meta-analysis. Diabetes Care 33: 931–939.
22. Schulz KF, Altman DG, Moher D (2010) CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 152: 726–732.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, et al. (2008) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 61: 344–349.
24. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, et al. (1999) Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 354: 1896–1900.
25. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, et al. (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 283: 2008–2012.
26. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, et al. (2009) The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 151: W65–94.
27. Bowker SL, Yasui Y, Veugelers P, Johnson JA (2010) Glucose-lowering agents and cancer mortality rates in type 2 diabetes: assessing effects of time-varying exposure. Diabetologia 53: 1631–1637.
28. Donadon V, Balbi M, Ghersetti M, Grazioli S, Perciaccante A, et al. (2009) Antidiabetic therapy and increased risk of hepatocellular carcinoma in chronic liver disease. World journal of gastroenterology : WJG 15: 2506–2511.
29. Donadon V, Balbi M, Mas MD, Casarin P, Zanette G (2010) Metformin and reduced risk of hepatocellular carcinoma in diabetic patients with chronic liver disease. Liver International 30: 750–758.
30. Yang X, So WY, Ma RC, Kong AP, Lee HM, et al. (2011) Low HDL cholesterol, metformin use, and cancer risk in type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care 34: 375–380.
31. He XX, Tu SM, Lee MH, Yeung SC (2011) Thiazolidinediones and metformin associated with improved survival of diabetic prostate cancer patients. Ann Oncol 22: 2640–2645.
32. Chen TM, Lin CC, Huang PT, Wen CF (2011) Metformin associated with lower mortality in diabetic patients with early stage hepatocellular carcinoma after radiofrequency ablation. Journal of gastroenterology and hepatology 26: 858–865.
33. Nkontchou G, Cosson E, Aout M, Mahmoudi A, Bourcier V, et al. (2011) Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. The Journal of clinical endocrinology and metabolism 96: 2601–2608.
34. Patel T, Hruby G, Badani K, Abate-Shen C, McKiernan JM (2010) Clinical outcomes after radical prostatectomy in diabetic patients treated with metformin. Urology 76: 1240–1244.
35. Bowker SL, Majumdar SR, Veugelers P, Johnson JA (2006) Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 29: 254–258.
36. Currie CJ, Poole CD, Gale EA (2009) The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 52: 1766–1777.
37. Hense HW, Kajuter H, Wellmann J, Batzler WU (2011) Cancer incidence in type 2 diabetes patients - first results from a feasibility study of the D2C cohort. Diabetology & metabolic syndrome 3: 15.
38. Landman GW, Kleefstra N, van Hateren KJ, Groenier KH, Gans RO, et al. (2010) Metformin associated with lower cancer mortality in type 2 diabetes: ZODIAC-16. Diabetes Care 33: 322–326.
39. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, et al. (2011) Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC cancer 11: 20.
40. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, et al. (2009) New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 32: 1620–1625.
41. Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L (2011) Prognostic implications of glucose-lowering treatment in patients with acute myocardial infarction and diabetes: experiences from an extended follow-up of the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 Study. Diabetologia 54: 1308–1317.
42. Morden NE, Liu SK, Smith J, Mackenzie TA, Skinner J, et al. (2011) Further exploration of the relationship between insulin glargine and incident cancer: a retrospective cohort study of older Medicare patients. Diabetes Care 34: 1965–1971.
43. Tseng CH (2011) Diabetes and risk of prostate cancer: a study using the National Health Insurance. Diabetes Care 34: 616–621.
44. Tseng CH (2011) Diabetes and risk of bladder cancer: a study using the National Health Insurance database in Taiwan. Diabetologia 54: 2009–2015.
45. Yang X, So WY, Ma RC, Yu LW, Ko GT, et al. (2010) Use of sulphonylurea and cancer in type 2 diabetes-The Hong Kong Diabetes Registry. Diabetes research and clinical practice 90: 343–351.
46. Home PD, Kahn SE, Jones NP, Noronha D, Beck-Nielsen H, et al. (2010) Experience of malignancies with oral glucose-lowering drugs in the randomised controlled ADOPT (A Diabetes Outcome Progression Trial) and RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes) clinical trials. Diabetologia 53: 1838–1845.
47. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, et al. (2006) Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med 355: 2427–2443.
48. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, et al. (2009) Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. Lancet 373: 2125–2135.
49. (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 352: 854–865.
50. Azoulay L, Dell'Aniello S, Gagnon B, Pollak M, Suissa S (2011) Metformin and the incidence of prostate cancer in patients with type 2 diabetes. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 20: 337–344.
51. Bodmer M, Meier C, Krahenbuhl S, Jick SS, Meier CR (2010) Long-term metformin use is associated with decreased risk of breast cancer. Diabetes Care 33: 1304–1308.

52. Bosco JL, Antonsen S, Sorensen HT, Pedersen L, Lash TL (2011) Metformin and incident breast cancer among diabetic women: a population-based case-control study in Denmark. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 20: 101–111.
53. Hassan MM, Curley SA, Li D, Kaseb A, Davila M, et al. (2010) Association of diabetes duration and diabetes treatment with the risk of hepatocellular carcinoma. Cancer 116: 1938–1946.
54. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL (2009) Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 137: 482–488.
55. Monami M, Lamanna C, Balzi D, Marchionni N, Mannucci E (2009) Sulphonylureas and cancer: a case-control study. Acta diabetologica 46: 279–284.
56. Monami M, Colombi C, Balzi D, Dicembrini I, Giannini S, et al. (2011) Metformin and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 34: 129–131.
57. Wright JL, Stanford JL (2009) Metformin use and prostate cancer in Caucasian men: results from a population-based case-control study. Cancer causes & control : CCC 20: 1617–1622.
58. Yang YX, Hennessy S, Lewis JD (2004) Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 127: 1044–1050.
59. Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ (2006) Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. Lancet 367: 1747–1757.
60. White MF (1997) The insulin signalling system and the IRS proteins. Diabetologia 40 Suppl 2: S2–17.
61. Kim YI (1998) Diet, lifestyle, and colorectal cancer: is hyperinsulinemia the missing link? Nutr Rev 56: 275–279.
62. Kaaks R (1996) Nutrition, hormones, and breast cancer: is insulin the missing link? Cancer Causes Control 7: 605–625.
63. Giovannucci E (1995) Insulin and colon cancer. Cancer Causes Control 6: 164–179.
64. Yu H, Berkel H (1999) Insulin-like growth factors and cancer. J La State Med Soc 151: 218–223.
65. Zhang W, Thornton WH, MacDonald RS (1998) Insulin-like growth factor-I and II receptor expression in rat colon mucosa are affected by dietary lipid intake. J Nutr 128: 158–165.
66. Bruning PF, Bonfrer JM, van Noord PA, Hart AA, de Jong-Bakker M, et al. (1992) Insulin resistance and breast-cancer risk. Int J Cancer 52: 511–516.
67. Hu FB, Manson JE, Liu S, Hunter D, Colditz GA, et al. (1999) Prospective study of adult onset diabetes mellitus (type 2) and risk of colorectal cancer in women. J Natl Cancer Inst 91: 542–547.
68. Silverman DT, Schiffman M, Everhart J, Goldstein A, Lillemoe KD, et al. (1999) Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer 80: 1830–1837.
69. Wolf I, Sadetzki S, Catane R, Karasik A, Kaufman B (2005) Diabetes mellitus and breast cancer. Lancet Oncol 6: 103–111.
70. Le Roith D (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Insulin-like growth factors. N Engl J Med 336: 633–640.
71. Richardson LC, Pollack LA (2005) Therapy insight: Influence of type 2 diabetes on the development, treatment and outcomes of cancer. Nat Clin Pract Oncol 2: 48–53.
72. Morss AS, Edelman ER (2007) Glucose modulates basement membrane fibroblast growth factor-2 via alterations in endothelial cell permeability. J Biol Chem 282: 14635–14644.
73. Barclay AW, Petocz P, McMillan-Price J, Flood VM, Prvan T, et al. (2008) Glycemic index, glycemic load, and chronic disease risk–a meta-analysis of observational studies. Am J Clin Nutr 87: 627–637.
74. Gapstur SM, Gann PH, Lowe W, Liu K, Colangelo L, et al. (2000) Abnormal glucose metabolism and pancreatic cancer mortality. JAMA 283: 2552–2558.
75. Seow A, Yuan JM, Koh WP, Lee HP, Yu MC (2006) Diabetes mellitus and risk of colorectal cancer in the Singapore Chinese Health Study. J Natl Cancer Inst 98: 135–138.
76. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, et al. (2005) Fasting serum glucose level and cancer risk in Korean men and women. JAMA 293: 194–202.
77. Stocks T, Rapp K, Bjorge T, Manjer J, Ulmer H, et al. (2009) Blood glucose and risk of incident and fatal cancer in the metabolic syndrome and cancer project (me-can): analysis of six prospective cohorts. PLoS Med 6: e1000201.
78. Abe R, Yamagishi S (2008) AGE-RAGE system and carcinogenesis. Curr Pharm Des 14: 940–945.
79. Inoue M, Kurahashi N, Iwasaki M, Tanaka Y, Mizokami M, et al. (2009) Metabolic factors and subsequent risk of hepatocellular carcinoma by hepatitis virus infection status: a large-scale population-based cohort study of Japanese men and women (JPHC Study Cohort II). Cancer Causes Control 20: 741–750.
80. Johnson JA, Gale EA (2010) Diabetes, insulin use, and cancer risk: are observational studies part of the solution-or part of the problem? Diabetes 59: 1129–1131.
81. Pocock SJ, Elbourne DR (2000) Randomized trials or observational tribulations? N Engl J Med 342: 1907–1909.
82. McFarland MS, Cripps R (2010) Diabetes mellitus and increased risk of cancer: focus on metformin and the insulin analogs. Pharmacotherapy 30: 1159–1178.
83. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, et al. (2008) Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab 93: 1834–1840.
84. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, et al. (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 89: 5462–5468.
85. Ding EL, Song Y, Malik VS, Liu S (2006) Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 295: 1288–1299.
86. Jalving M, Gietema JA, Lefrandt JD, de Jong S, Reyners AK, et al. (2010) Metformin: taking away the candy for cancer? European journal of cancer 46: 2369–2380.
87. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, et al. (2009) Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 27: 3297–3302.
88. Hosono K, Endo H, Takahashi H, Sugiyama M, Uchiyama T, et al. (2010) Metformin suppresses azoxymethane-induced colorectal aberrant crypt foci by activating AMP-activated protein kinase. Molecular carcinogenesis 49: 662–671.
89. Piccinni C, Motola D, Marchesini G, Poluzzi E (2011) Assessing the Association of Pioglitazone Use and Bladder Cancer Through Drug Adverse Event Reporting. Diabetes Care.
90. Lewis JD, Ferrara A, Peng T, Hedderson M, Bilker WB, et al. (2011) Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. Diabetes are 34: 916–922.
91. Giovannucci E (2007) Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. The American journal of clinical nutrition 86: s836–842.
92. Zakikhani M, Dowling RJ, Sonenberg N, Pollak MN (2008) The effects of adiponectin and metformin on prostate and colon neoplasia involve activation of AMP-activated protein kinase. Cancer prevention research 1: 369–375.
93. Algire C, Amrein L, Zakikhani M, Panasci L, Pollak M (2010) Metformin blocks the stimulative effect of a high-energy diet on colon carcinoma growth in vivo and is associated with reduced expression of fatty acid synthase. Endocrine-related cancer 17: 351–360.
94. Raimondi S, Maisonneuve P, Lowenfels AB (2009) Epidemiology of pancreatic cancer: an overview. Nature reviews Gastroenterology & hepatology 6: 699–708.
95. Schneider MB, Matsuzaki H, Haorah J, Ulrich A, Standop J, et al. (2001) Prevention of pancreatic cancer induction in hamsters by metformin. Gastroenterology 120: 1263–1270.
96. Xue F, Michels KB (2007) Diabetes, metabolic syndrome, and breast cancer: a review of the current evidence. The American journal of clinical nutrition 86: s823–835.
97. Memmott RM, Mercado JR, Maier CR, Kawabata S, Fox SD, et al. (2010) Metformin prevents tobacco carcinogen-induced lung tumorigenesis. Cancer prevention research 3: 1066–1076.
98. Yang YX (2009) Do diabetes drugs modify the risk of pancreatic cancer? Gastroenterology 137: 412–415.

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第53回日本老年医学会学術集会記録
〈若手企画シンポジウム2：サルコペニア―研究の現状と未来への展望―〉

# 6. Sarcopenic Obesity―代謝からみたサルコペニアの意義―

荒木　厚　周　赫英　森　聖二郎

Key words：高齢者，サルコペニア，糖尿病，インスリン抵抗性，炎症

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## はじめに

サルコペニアは①筋肉量の減少，および②筋力または筋のパフォーマンスの低下と定義されてきている．一方，sarcopenic obesityはサルコペニアと肥満の両者が合併したものである．未だサルコペニアの定義と肥満の定義が研究によって異なるために，機能的予後，動脈硬化性疾患を予測できるかについては，未だ意見の一致を見ていない．本稿ではsarcopenic obesityについて概説するとともに，高齢糖尿病患者を対象に，DXA（Dual energy X-ray absorpiometry）法の筋肉量と体脂肪量より定義したsarcopenicとインスリン抵抗性，身体機能，および転倒との関連について報告する．また，sarcopenic obesityとサルコペニアとの相違点についても考察してみたい．

## Sarcopenic obesityの頻度

DXA法により，四肢の筋肉量（appendicular skeletal mass）を身長の2乗で割ったRelative Skeletal Muscle Index（RSMI）を用いてサルコペニアを評価した場合，高齢者のsarcopenic obesityの頻度は5～10%であり，80歳以上になると10%を越える[1)~3)]．New Mexico Aging Studyは831名の60歳以上住民を対象に，サルコペニアを若い人のRSMIの平均－2SD以下と定義（男性で7.26 kg/m$^2$未満，女性で5.45 kg/m$^2$未満）し，肥満を体脂肪率のメディアン以上と定義すると，その頻度は男性で4.4%，女性で3.0%であった[1)]．NHANES III研究では2,982名（平均年齢77歳）を対象にサルコペニア：RSMIの5分位の下2分位（男性で9.12 kg/m$^2$未満，女性で6.53 kg/m$^2$未満），肥満を体脂肪率の5分位の上2分位と定義するとその頻度は男性で9.6%，女性で7.4%であった[2)]．

われわれは，2008年～2010年に入院し，DXA法で全身骨密度検査の検査を受けた入院糖尿病患者93名（年齢：74.9±8.3歳，男35名，女性58名，BMI：23.5±4.0，罹病年数：16.5±11.3年，HbA1c：8.2±1.6%，治療法：食事のみ11名，経口薬55名，インスリン27例）を対象としてsarcopenic obesityの頻度を算出した．サルコペニアはRSMI＝appendicular lean mass ÷ (height)$^2$のmedian未満または5分位の下2分位と定義し，肥満は体脂肪率，BMI，または内臓脂肪面積で定義した．サルコペニアをRSMIのmedian未満と定義した際のカットオフ値は男性で6.53 kg/m$^2$未満，女性で5.72 kg/m$^2$であった．体脂肪率の5分位の上2分位を肥満と定義すると肥満の頻度は39.6%であった．BMI 24以上を肥満と定義すると肥満の頻度は42%であった．内臓脂肪面積100 cm$^2$以上と定義すると，内臓脂肪肥満の頻度は34.4%であった．こうした3種類の肥満の定義とサルコペニアを組み合わせてsarcopenic obesityを定義するとその頻度はそれぞれ16.7%，12.5%，14.6%であり，体脂肪率とDXA法のRSMI median以下を組み合わせて使った場合の頻度が最も多かった．しかし，sarcopenic obesityの肥満の定義を体脂肪，BMI，内臓脂肪量のいずれを用いるべきかについての報告はない．

サルコペニアの定義も筋量のみで定義するよりは「筋量低下かつ筋力低下また身体能力の低下」と変わりつつある[4)]．これは脂肪の筋肉へ浸潤の影響を考慮して，筋量が正確に測定できていない場合があることや筋肉の量よりも筋肉の機能の方が機能的予後を反映しやすいということに基づいている．

## Sarcopenic obesityの成因・機序

Sarcopenic obesityを構成するサルコペニアと肥満の

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Relationship between sarcopenic obesity or sarcopenia and insulin resistance or functional disability

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