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ORIGINAL ARTICLE

Association between hyperglycaemia and fracture risk in non-diabetic middle-aged and older Australians: a national, population-based prospective study (AusDiab)

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Abstract
Summary The association between pre-diabetes and fracture risk remains unclear. In this large cohort of middle-aged and older Australian men and women without diabetes, elevated 2-h plasma glucose and pre-diabetes were associated with a reduced 5-year risk of low trauma and all fractures in women, independently of BMI, fasting insulin and other lifestyle factors.
Introduction We aimed to (1) examine associations between fasting and 2-h plasma glucose (FPG and 2-h PG), fasting insulin and risk of low trauma and all fractures in non-diabetic adults and (2) compare fracture risk between adults with pre-diabetes (impaired glucose tolerance or impaired fasting glucose) and those with normal glucose tolerance (NGT).
Methods Six thousand two hundred fifty-five non-diabetic men and women aged ≥40 years with NGT (n=4,855) and pre-diabetes (n=1,400) were followed for 5 years in the AusDiab Study. Fractures were self-reported.
Results Five hundred thirty-nine participants suffered at least one fracture (368 women, 171 men), of which the majority (318) occurred after a low-energy trauma (258 women, 60 men). In women, a 2-h PG ≥7.2 mmol/L (highest quartile) was associated with a decreased risk of low trauma and all fractures independent of age and BMI [OR (95% CI) for low trauma fractures, 0.59 (0.40–0.88)], but also fasting insulin, smoking, physical activity, history of fracture, dietary calcium and alcohol intake or menopausal status. There was no effect of 2-h PG on fracture risk in men [OR (95% CI), 1.39 (0.60–3.26)] or any relationship between fracture risk and quartiles of FPG or insulin in either sex. Compared to women with NGT, those with pre-diabetes had a reduced risk of fracture [OR (95% CI) for all fractures, 0.70 (0.52–0.95); for low trauma fractures, 0.75 (0.53–1.05)].
Conclusion Elevated 2-h PG levels and pre-diabetes were inversely associated with low trauma and/or all fractures in non-diabetic women, independent of BMI and fasting insulin levels.

Keywords Fractures · Glycemia · Insulin · Pre-diabetes

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Introduction

In recent years, several epidemiological studies have reported a link between type 2 diabetes and an increased risk of fragility fractures [1–3] despite reports that bone

mineral density (BMD) is elevated [4]. Diabetes duration may modulate fracture risk as people with newly diagnosed type 2 diabetes were found to be at reduced risk of fractures in a large retrospective study [5]. This suggests that the increased fracture risk associated with type 2 diabetes may be due to either an increased propensity to fall, related to diabetes complications and medications [6, 7], and/or alterations in bone quality resulting from the accumulation of advanced glycation end-products in bone collagen [8].

It is unclear, however, whether people with pre-diabetes share the same increased risk of fractures as people with type 2 diabetes. Data from the few studies reporting fracture risk in people with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) have been inconsistent [1, 2]. In men and women without diabetes, Holmberg et al. [9] reported that a higher 2-h plasma glucose level (2-h PG) was associated with a reduction in fracture risk, which they attributed to the anabolic effect of hyperinsulinaemia on bone. However, fasting insulin, which was only measured in a subset of the participants undergoing oral glucose tolerance testing (OGTT), was not associated with fracture risk in this study.

We hypothesise that contrary to what has been observed in people with diabetes, those with pre-diabetes will not be at increased risk of fractures. Although they typically display higher BMD [1, 2], adults with pre-diabetes do not present the same falls risk factors and have not been exposed to the same degree and duration of hyperglycaemia as those with type 2 diabetes. Therefore, the primary aim of this study was to investigate associations between fasting plasma glucose (FPG) and 2-h PG, fasting insulin and fracture risk in a large population-based cohort of non-diabetic middle-aged and older Australian men and women. A secondary aim was to assess whether fracture risk was increased in people with pre-diabetes (IGT or IFG).

Research design and methods

Subjects

The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) is a prospective, population-based study that was initiated in 1999–2000 to determine the prevalence and incidence of diabetes and pre-diabetes across Australia using the 2-h OGTT. The AusDiab methods have been described in detail elsewhere [10]. Briefly, from the 17,129 eligible households, 20,347 non-institutionalised adults aged ≥25 years completed a household interview and 11,247 (55.3%) attended a biomedical evaluation, giving an overall response rate of 37%. Of those who took part in the biomedical evaluation at baseline, 8,767 (78%) completed a fracture questionnaire at the 5-year visit. People aged ≥40 years that were free of diabetes at baseline were included in this analysis (n=6,255; 2,770 men and 3,485 women). FPG, 2-h PG and fasting insulin were available for all participants. Written informed consent was obtained from all participants, and ethical approval was provided by the International Diabetes Institute Ethics Committee and the Standing Committee on Ethics in Research Involving Humans.

Measurements

Risk factors

Data on age, sex, smoking, physical activity and menopausal status were collected by trained interviewers using standardised questionnaires. Smoking status was categorised into "current smoker", "ex-smoker" and "non-smoker". Women were classified as "premenopausal" or "menopausal" based on self-report at baseline. Total leisure time physical activity reported for the previous week (minutes/week) was measured using the Active Australia questionnaire [11], a reliable and validated questionnaire [12]. A self-administered validated food frequency questionnaire developed by the Anti-Cancer Council of Victoria was used to assess nutrient intake, including daily calcium and alcohol intake [13]. Calculation of nutrient intake was achieved by multiplying the frequency of consumption by standard portion weights which were then converted into nutrient intakes based on the NUTTAB95 nutrient composition database [14]. Alcohol intake was categorised into <3 or ≥3 units (30 g) per day [15].

Anthropometry

Weight was measured without shoes and in light clothing to the nearest 0.1 kg using a mechanical beam balance. Height was measured to the nearest 0.5 cm without shoes using a stadiometer. Body mass index (BMI) was calculated in kilograms per square metre. Waist circumference was measured using a steel measuring tape halfway between the lower border of the ribs and the iliac crest on a horizontal plane. Hip circumference was measured at the widest point over the buttocks. Duplicate measurements were taken to the nearest 0.5 cm. Waist-to-hip ratio (WHR) was obtained by dividing the mean waist circumference by the mean hip circumference.

Laboratory analyses

Blood was drawn after an overnight fast (≥9 h) for measurement of glucose and insulin followed by a 2-h 75 g OGTT. Serum samples for insulin were stored at −80°C until assayed. All specimens were analysed at a central laboratory.

FPG and 2-h PG were analysed by an automated glucose oxidase method (Olympus Optical Co. Ltd., Tokyo, Japan). Serum insulin was measured using a human insulin-specific radioimmunoassay kit (LincoResearch Inc., St Charles, MO, USA).

Classifications of glucose tolerance status

Participants were classified as having IFG, IGT or normal glucose tolerance (NGT) based on the 1999 World Health Organisation criteria: IFG (FPG 6.1–6.9 mmol/L with 2-h PG <7.8 mmol/L), IGT (FPG <7.0 mmol/L with 2-h PG 7.8–11.0 mmol/L) or NGT (FPG <6.1 mmol/L with 2-h PG <7.8 mmol/L) [16]. People with IFG and IGT formed the pre-diabetes group.

Fracture assessment

Data on fractures were self-reported and collected via an interviewer-administered questionnaire as part of the 5-year follow-up. Specifically, interviewers asked the participant "if a doctor ever told them that they had broken or fractured any bone since age 25". The participant was also asked to provide details about the specific site, cause and age at which any fracture had occurred. Fracture sites were coded as hip, rib, forearm, wrist, hand, spine, ankle, humerus, leg, clavicle, foot, pelvis and other. Fractures were classified as either low-energy (e.g. fall from standing height or less; n=318) or high-energy trauma (e.g. resulting from a harder fall, a car accident or other severe trauma; n=221). Low-trauma fractures that occurred between the baseline and 5-year follow-up visit were used as the primary outcome to calculate incident fractures, but all incident fractures were considered in a secondary analysis [17]. Participants who reported sustaining a low-trauma fracture(s) before the baseline visit were classified as having a history of low-trauma fractures. In the Women's Health Initiative Study, a validation study of self-reported fractures showed that there was good agreement between self-report and fractures of the hip (78%) and forearm/wrist (81%), but lower agreement for clinical spine fractures (51%) [18].

Statistical analysis

Analyses were performed using SPSS 17.0 for Windows (Chicago, IL, USA). Variables that were not normally distributed were log-transformed prior to analysis (FPG, 2-h PG and fasting insulin). Statistical differences in baseline characteristics between quartiles of FPG, 2-h PG and fasting insulin were determined using a chi-square test, ANOVA (or Kruskal–Wallis test) and with Tukey post hoc tests. To evaluate the effect of FPG, 2-h PG and fasting insulin on fracture risk, a logistic regression model was used with the presence or absence of a low trauma (primary outcome) and all fractures (secondary outcome) during follow-up as the dependent variable. FPG, 2-h PG and fasting insulin were entered as quartiles and also as continuous variables in the model. Since a significant interaction between sex and quartiles of FPG, 2-h PG and fasting insulin was found (P<0.001), men and women were analysed separately. The relationship between pre-diabetes and fracture risk was assessed using the same model. Odds ratios were calculated with corresponding 95% confidence intervals [OR (95% CI)]. In all models, the results were presented as unadjusted and adjusted for potential confounders: age, BMI (or WHR), smoking status, history of low-trauma fracture, menopausal status in women, physical activity, fasting insulin, alcohol and dietary calcium intake. A P value <0.05 was considered statistically significant.

Results

Incident fractures

Overall, 539 participants (368 women, 171 men) reported at least one clinical fracture during the 5-year follow-up period, of which 318 (258 women, 60 men) were sustained after a low-energy trauma. The proportion of men with high energy fractures was more than twice as high as that in women (29.9% women, 64.3% men). The majority of participants who sustained a clinical fracture experienced only one low-trauma fracture (89.9% women, 93.3% men). Wrist/forearm fractures were the most common (26.1%), followed by fractures of the foot (12.9%), ribs (12.3%) and spine (11.0%). Humerus and hip fractures represented 4.4% and 5.3% of the reported fractures, respectively. Fractures of the wrist/forearm were more common in women than men (29.1% vs. 13.3%, P=0.01), whilst rib fractures occurred more frequently in men (30% vs. 8.1%, P< 0.001). No difference in anthropometry, lifestyle risk factors or glucose and insulin levels was seen between men and women who fractured compared to those who did not fracture during follow-up (Table 1). However, men and women who fractured were older, and women with a history of low-trauma fracture and those who were menopausal at baseline were more likely to fracture.

Baseline characteristics of men and women across quartiles of FPG, 2-h PG and fasting insulin followed similar trends. Age, BMI and fasting insulin levels increased with each quartile of FPG and 2-h PG. The proportion of current smokers was higher in men and women in the lowest quartile of 2-h PG as well as in men in the lowest quartile of fasting insulin (18.6% vs. 12.1%, P<0.001). Leisure time physical activity decreased significantly across quartiles of 2-h PG and fasting insulin in

Table 1 Baseline characteristics of the 6,243 men and women aged 40 and over by incident low-trauma fractures

	Men		Women	
	Fracture	No fracture	Fracture	No fracture
n	60	2,710	258	3,227
History of fractures (%)	8.3	4.9	17.1**	9.6
Age (years)	58.9±10.9*	55.6±10.7	62.2±11.2**	54.9±10.7
BMI (kg/m^2)	27.6±4.3	27.1±3.8	26.2±4.6	26.8±5.2
Ex/Current smoking (%)	49.2/13.6	38.9/13.7	25.4/10.2	23.4/11.3
Physical activity (min/week)[a]	285±295	327±365	232±284	230±285
Fasting plasma glucose (mmol/L)	5.6±0.5	5.6±0.5	5.3±0.5	5.3±0.5
2-h plasma glucose (mmol/L)	6.1±1.7	6.0±1.6	6.2±1.7	6.1±1.6
Fasting insulin (pmol/L)	95.5±41.4	98.9±55.4	88.6±33.7	93.4±47.2
Alcohol consumption (%)[b]	30.9	24.1	7.5	5.4
Calcium intake (mg/day)	878±332	908±352	862±345	871±346
Menopause (%)	–	–	89.5**	69.1

Data are mean ± SD and proportion (%)

BMI body mass index

[a] Leisure time physical activity assessed by the Active Australia questionnaire

[b] ≥3 units (30 g) of alcohol per day assessed by food frequency questionnaire

*P<0.05; **P<0.001 (compared to no fracture)

both men and women. The proportion of women who had a history of fractures, as well as the percentage of postmenopausal women, rose significantly over quartiles of FPG (from 63.2% to 78.8%, P<0.001), 2-h PG and fasting insulin. Men in the third and fourth quartiles of FPG were more inclined to drink more than 3 units of alcohol daily than those in the lowest quartile (26.9% and 29.6% vs. 19.1%, respectively, P<0.001). Daily dietary calcium intakes decreased progressively over quartiles of FPG and 2-h PG in men only. Since only 2-h PG was associated with fracture risk in the regression model, the baseline characteristics by quartiles of 2-h PG are presented in Table 2.

Independent associations of FPG, 2-h PG and fasting insulin with fracture risk

The unadjusted and age- and BMI-adjusted OR (95% CI) for low-trauma fractures in men and women by quartiles of FPG, 2-h PG and fasting insulin are shown in Table 3 and Fig. 1. In women, the adjusted OR for fracture risk did not change significantly across quartiles of FPG or fasting insulin. However, women in the highest quartile of 2-h PG were at significantly lower risk of fracture than those in the lowest quartile [0.59 (0.40–0.88), after adjustment for age and BMI]. Substituting BMI for waist or hip circumference (or the WHR) in the regression model or including a history of low-trauma fracture, fasting insulin or menopausal status did not significantly affect the ORs. Similarly, after adding smoking status, physical activity, alcohol and dietary calcium into the multivariate model, the results remained significant. Results were similar when all fractures were considered or whether FPG, 2-h PG and fasting insulin were considered as continuous variables in the model. In men, there was no effect of FPG and 2-h PG on fracture risk. There was a trend for men in the third quartile of fasting insulin to be at reduced risk of fractures (P=0.05), but this was not seen in the fourth quartile.

Pre-diabetes status at baseline as a predictor of incident fractures

In women, there was a trend for the age- and BMI-adjusted risk of low trauma fracture to be reduced in those with pre-diabetes at baseline compared to those with NGT [0.75 (0.53–1.05)]. This association became significant when BMI was replaced by WHR [0.69 (0.49–0.96)] and when all incident fractures were considered [age- and BMI-adjusted, 0.70 (0.52–0.95), and age- and WHR-adjusted, 0.66 (0.49–0.88)]. Similar results were observed after including other covariates in the model. The presence of pre-diabetes at baseline did not influence fracture risk in men [0.85 (0.46–1.57)].

Discussion

In this cohort of middle-aged and older Australian men and women without diabetes, we found that elevated 2-h PG levels and the presence of pre-diabetes at baseline were associated with a lower incidence of low trauma and all clinical fractures in women after adjusting for multiple independent confounders including age, BMI, smoking, menopausal status, physical activity, history of low-trauma fractures, fasting insulin and dietary calcium and alcohol intake. Specifically, women in the highest quartile of 2-h PG (≥7.2 mmol/L) had a 37% to 41% decreased risk of low trauma or all clinical fractures at 5 years compared to those in the lowest quartile. Neither fasting insulin nor FPG was associated with fracture risk.

Table 2 Baseline characteristics of the 6,243 men and women aged 40 and over by quartiles of 2-h PG

	First quartile (<4.9 mmol/L)	Second quartile (4.9–5.7 mmol/L)	Third quartile (5.8–6.8 mmol/L)	Fourth quartile (6.9–11.0 mmol/L)	*P* value[a]
Men (*n*)	690	687	699	690	
Fractures during follow-up (%)[b]	1.3	2.8	2.1	2.3	0.3
History of fractures (%)	4.2	4.9	4.6	6.2	0.3
Age (years)	53.3±9.8	54.2±10.0	55.6±10.6	59.4±11.3	<0.001
BMI (kg/m^2)	26.3±3.5	26.5±3.6	27.4±3.7	28.2±4.0	<0.001
Ex/Current smoking (%)	36.8 / 18.0	35.5 / 12.9	36.8 / 14.1	47.4 / 9.7	<0.001
Physical activity (min/week)[c]	358±385	330±367	338±368	279±327	<0.01
Fasting insulin (pmol/L)	85.3±35.3	91.2±39.7	98.8±47.1	120.2±80.5	<0.001
Alcohol consumption (%)[d]	27.1	22.3	22.5	24.9	0.1
Calcium intake (mg/day)	953±360	910±350	915±349	857±339	<0.001
	First quartile (<5.1 mmol/L)	Second quartile (5.1–5.9 mmol/L)	Third quartile (6.0–7.1 mmol/L)	Fourth quartile (7.2–11.0 mmol/L)	
Women (*n*)	900	873	860	844	
Fractures during follow-up (%)[b]	7.8	7.4	7.4	7.0	0.9
History of fractures (%)	7.7	9.7	12.1	11.1	<0.01
Age (years)	52.1±9.6	54.2±10.2	56.4±11.2	59.1±11.4	<0.001
BMI (kg/m^2)	24.9±4.4	26.2±4.8	27.2±5.1	28.7±5.6	<0.001
Ex/Current smoking (%)	26.5/14.6	22.0/12.4	23.9/8.3	21.6/9.4	<0.001
Menopause (%)	61.5	69.2	73.2	79.2	<0.001
Physical activity (min/week)[c]	270±307	248±290	224±291	178±235	<0.001
Fasting insulin (pmol/L)	77.0±31.4	87.9±37.7	96.7±45.8	110.9±58.7	<0.001
Alcohol consumption (%)[d]	4.9	6.6	5.9	4.9	0.4
Calcium intake (mg/day)	873±323	869±357	865±354	875±346	0.9

Data are mean ± SD and proportion (%)

BMI body mass index

[a] *P* value for the trend across quartiles of 2-h PG using a chi-square test, ANOVA or Kruskal–Wallis test

[b] Low-trauma fractures

[c] Leisure time physical activity assessed by the Active Australia questionnaire

[d] ≥3 units (30 g) of alcohol per day assessed by food frequency questionnaire

Table 3 Unadjusted and adjusted odds ratio (95% CI) for incident low-trauma fractures in men and women by quartiles of 2-h PG

	Men			Women		
	2nd quartile	3rd quartile	4th quartile	2nd quartile	3rd quartile	4th quartile
Unadjusted	2.15 (0.97–4.79)	1.66 (0.72–3.82)	1.80 (0.79–4.09)	0.95 (0.67–1.36)	0.95 (0.67–1.36)	0.89 (0.62–1.28)
Adjusted for						
Age	2.10 (0.94–4.69)	1.55 (0.67–3.58)	1.51 (0.65–3.49)	0.83 (0.58–1.18)	0.70 (0.49–1.01)	0.56 (0.38–0.81)
Age and BMI	2.08 (0.93–4.64)	1.49 (0.64–3.44)	1.39 (0.60–3.26)	0.85 (0.59–1.21)	0.73 (0.50–1.05)	0.59 (0.40–0.88)
Age and history of fractures	2.10 (0.94–4.69)	1.56 (0.68–3.60)	1.50 (0.65–3.47)	0.82 (0.57–1.17)	0.69 (0.48–1.00)	0.55 (0.38–0.81)
Age and menopausal status	–	–	–	0.83 (0.58–1.19)	0.72 (0.50–1.03)	0.56 (0.38–0.82)
Age and fasting insulin	2.13 (0.96–4.75)	1.60 (0.69–3.69)	1.59 (0.68–3.74)	0.84 (0.58–1.20)	0.72 (0.50–1.04)	0.57 (0.39–0.85)
Multivariate model 1[a]	2.13 (0.95–4.74)	1.54 (0.66–3.57)	1.50 (0.64–3.54)	0.85 (0.59–1.22)	0.74 (0.51–1.08)	0.60 (0.40–0.89)
Multivariate model 2[b]	2.34 (0.99–5.49)	1.78 (0.73–4.32)	1.68 (0.68–4.16)	0.95 (0.65–1.39)	0.80 (0.54–1.18)	0.65 (0.43–0.99)

[a] Adjusted for age, BMI, history of fractures, fasting insulin and postmenopausal status in women

[b] Adjusted for age, BMI, history of fractures, fasting insulin, postmenopausal status in women, smoking status, physical activity, calcium and alcohol intake

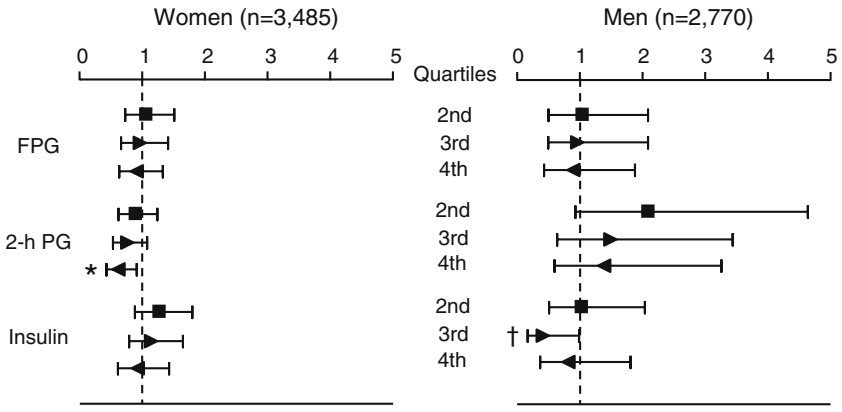

Fig. 1 Age- and BMI-adjusted odds ratio (95% CI) for incident low-trauma fractures according to quartiles of fasting plasma glucose (*FPG*), 2-h plasma glucose (*2-h PG*) and fasting insulin in men and women. *$P<0.01$ vs. first quartile. †$P=0.05$ vs. first quartile

In a similar study involving middle-aged non-diabetic people in Sweden, increased 2-h PG levels were found to be associated with a reduction in incident multiple fractures in both men (ORs 0.57–0.71) and women (ORs 0.38–0.66), independent of age, BMI and smoking [9]. However, only women in the fourth quartile of 2-h PG (≥7.5 mmol/L) were at significantly reduced risk of osteoporotic fractures [0.57 (0.44–0.74)]. The magnitude of this effect in women is similar to our results, even though our follow-up period was shorter (5 vs. 15 years). Nevertheless, our study confirms and adds to these findings by demonstrating that the relationship between 2-h PG and fracture risk remained significant even after adjusting for other important confounders, including fasting insulin which was only assessed in a subset of the Swedish participants. This is important because the authors of this study hypothesised that the reduction in fracture risk was likely due to the anabolic effect of hyperinsulinaemia on bone [9]. Our findings suggest that the relationship between 2-h PG and fracture risk was independent of serum insulin levels. Nevertheless, it is difficult to compare the results from these studies because the limited number of incident fractures in women in our study did not allow for grouping into osteoporotic (or multiple) fractures. In addition, the finding that there was no association between the presence of FPG, 2-h PG or fasting insulin and fracture risk in the men in our study is most likely due to the small number of events compared with the Swedish study (60 vs. 1,246 incident low-trauma fractures).

Few studies have evaluated whether people with pre-diabetes share the same increased risk of fractures compared with people with type 2 diabetes. In the Rotterdam Study which examined the association between type 2 diabetes and fractures in 6,655 men and women aged 55 years and over who were stratified according to different levels of insulin resistance, people with IGT had a reduced risk of fractures when compared to those with NGT [HR 0.80 (0.63–1.00)] even after adjusting for multiple confounders including BMD [2]. On the other hand, a non-significant 30% increase in fracture risk was observed in people with IFG participating in the Health ABC Study which was a prospective (mean ± SD follow-up, 4.5± 1.1 years) cohort study in well-functioning, community-dwelling older adults [1]. However, the participants in this study were older (70–79 years), a large proportion were non-Caucasian and the number with IFG was small ($n=177$), all of which may have contributed to the increased risk. In our study, there was also a trend for the age- and BMI-adjusted risk of low-trauma fractures to be reduced in women with pre-diabetes at baseline [OR 0.75 (0.53–1.05)]. Whilst the magnitude of the risk reduction was similar to the Rotterdam Study, the lack of statistical significance in our study is likely due to the small number of fractures reported among women with pre-diabetes ($n=49$). Indeed, when the analyses included all incident fractures, the presence of pre-diabetes was a significant independent predictor of fractures in women after adjustment for age and BMI [OR 0.70 (0.52–0.95)] and other covariates including insulin.

We can only speculate on the mechanisms by which elevated 2-h PG, but not FPG levels, have a protective effect on fracture risk in adults without diabetes. The hyperinsulinaemia that accompanies insulin resistance and pre-diabetes could increase BMD by stimulating bone formation [19]. However, our findings and those by Holmberg et al. [9], which both included middle-aged and older non-diabetic adults, revealed that fasting insulin did not impact on fracture risk. It is possible, however, that post load insulin levels could lead to different results because hormones released after nutrient absorption, such as glucagon-like peptide-1, have been shown to increase expression of the osteoblast-derived protein, osteocalcin (OC), in insulin-resistant and diabetic rats [20]. Of interest, OC was recently identified as a new factor controlling glucose metabolism via regulation of both β-cell insulin secretion and adiponectin [21]. Osteocalcin knockout mice ($OC^{-/-}$) were overweight and glucose-intolerant, had reduced β-cell mass and pancreatic insulin content,

decreased adiponectin expression and low serum adiponectin levels, similar to humans with type 2 diabetes. Uncarboxylated OC (ucOC) was the metabolically active form which induced expression of adiponectin in adipocytes [21]. Moreover, increased ucOC levels have been shown to independently predict fracture risk in postmenopausal women, whilst serum adiponectin levels were inversely and independently associated with BMD in women after adjustment for BMI, fat mass and insulin levels [22, 23]. Collectively, these findings suggest that decreased serum ucOC and/or adiponectin levels in people with elevated 2-h glucose could mediate the beneficial effects on bone. Nevertheless, it remains unclear why people with type 2 diabetes are at increased risk of fractures whilst those with elevated 2-h glucose levels without diabetes are protected against fractures. Both groups benefit from an increased BMD, but factors such as medication and diabetes complications may expose people with type 2 diabetes to a greater risk of falls [6, 24]. The degree and duration of exposure to hyperglycaemia may also contribute to decreased bone quality in people with type 2 diabetes by increasing glycoxidative (non-enzymatic) pentosidine cross-links of collagen which have recently been shown to predict vertebral fractures in elderly women [25].

The strengths of our study include the recruitment of a large national, population-based sample of Australian men and women across a broad age range along with the direct diagnosis of diabetes using an objective measure (OGTT) and the evaluation of a large number of important confounders. However, there are a number of limitations. First, ascertainment of fractures was based on self-report only. Whilst this method may have underestimated the incidence of vertebral fractures, a good agreement has been reported between self-report and fractures of the wrist/forearm [3], which represented more than 25% of all fractures in our study. Furthermore, repeating the analysis with the inclusion of all incident fractures produced equivalent results. Second, we cannot ascertain whether the relationship between 2-h PG and fracture incidence differs by sex because of the small number of incident fractures occurring in men in our study. Third, BMD and falls risk were not assessed in our study, which are key predictors of fractures. However, previous research has shown that the inclusion of BMD as a covariate does not significantly affect fracture risk in people with IGT [2]. This suggests that other determinants of bone strength, including bone structure, may be compromised in these patients [2]. Finally, no data were collected on medication or calcium–vitamin D supplement use, which might affect bone metabolism. Possible bias by residual confounding also cannot be excluded.

In conclusion, this study indicates that elevated 2-h PG levels and pre-diabetes were associated with a reduced risk of low trauma and all clinical fractures in non-diabetic middle-aged and older women, independent of BMI and fasting insulin levels. Given that type 2 diabetes tends to be associated with an increased fracture risk, further studies are needed to better understand the underlying mechanisms which could explain these contrasting results.

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Conflicts of interest None.

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