Letters

How many cases of Type 2 diabetes mellitus are due to being overweight in middle age? Evidence from the Midspan prospective cohort studies using mention of diabetes mellitus on hospital discharge or death records

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Hart *et al*. are to be commended on another interesting result from the landmark Renfrew/Paisley study which has yielded so much of benefit [1]. However, in their interpretation of the data they have omitted a further explanation which is kinder to the victim of Type 2 diabetes and also in keeping with current scientific data on obesity. The possibility that some of the genetic influences responsible for Type 2 diabetes [2] also influence whether its sufferers become overweight during their lifetime was not discussed. However, it is generally accepted that people who develop Type 2 diabetes have a tendency to acquire fat centrally, and for 80–90% to be overweight or obese. In agreement with Stunkard's landmark studies showing body mass index (BMI) heritability, we have reported the strong heritability of both total and central fat mass in healthy humans [3–5].

We have also recently reported a potential mechanism influencing later weight gain [6]. In healthy normoglycaemic relatives of Type 2 diabetic subjects, we found significantly lower fasting PYY levels than in control subjects matched for age, gender and adiposity without such relatives. This lack of a satiety factor could contribute to later weight gain, which can itself hasten onset of Type 2 diabetes by several mechanisms. For example, we have also reported, in insulin resistant normoglycaemic Type 2 diabetic relatives, a decrease over 6 years in insulin secretion which related only to their increase in central fat.

There is an implication in the paper that the weight gain occurs independent of the disease and could hence be dealt with easily by a 'serious' attempt at weight loss in the general population, hence preventing Type 2 diabetes. If so, could the authors indicate the papers showing such permanent weight loss in the healthy population maintained over more than 5 years? People who are obese continually try to lose weight, with and without medical help. The reason it is not easily achieved is because of the strong heritability.

Thus, I suggest that statistically the predictive relationship is strong between BMI and later diabetes, both for the reasons the authors mention and because there may be shared genetic factors linking adiposity and Type 2 diabetes.

Competing interests

None to declare.

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Authors' response

Lesley Campbell suggests an interesting hypothesis that 'there may be shared genetic factors linking adiposity and Type 2 diabetes' and that acknowledging this is 'kinder to the victim of Type 2 diabetes'. She suggests that rather than overweight causing Type 2 diabetes, genetic factors might predispose to both Type 2 diabetes and weight gain. Consequently, a public health message to reduce weight in order to prevent diabetes would have limited impact. Whilst there is considerable evidence from heritability studies that both obesity and Type 2 diabetes are complex diseases with genetic and environmental causes, Campbell provides no evidence of the hypothesis that a single genetic variant or group of variants cause both obesity and Type 2 diabetes and therefore explain the link between the two.

The strongest evidence for obesity being causally related to Type 2 diabetes comes from both randomized controlled trials and genetic association studies, when a Mendelian randomization approach is applied to these studies. Amongst individuals at high risk of diabetes (overweight and/or with impaired glucose tolerance), randomized controlled trial

evidence demonstrates that lifestyle interventions aimed at weight loss are effective at reducing Type 2 diabetes risk [1,2], with this effect being greater than the effect of metformin alone [2]. The reduction in risk in these trials is largely attributable to weight reduction in the intervention group. A Cochrane systematic review concluded that 'Overall, weight loss strategies using dietary, physical activity, or behavioural interventions produced significant improvements in weight among persons with pre-diabetes and a significant decrease in diabetes incidence' [3].

A recent genome-wide association study for Type 2 diabetes susceptibility identified a variant in the *FTO* gene that predisposes to Type 2 diabetes via an effect on body mass index (BMI) [4]. An additive effect of the variant on BMI, replicated in 13 unselected independent population studies with 38 759 participants, was demonstrated such that each A allele was associated with a mean difference in BMI z-score of 0.10 (95% CI 0.08, 0.12; $P = 2 \times 10^{-20}$) [4]. The per allele effect on odds of diabetes was 1.15 (95% CI 1.09, 1.23; $P = 9 \times 10^{-6}$) and this was essentially abolished upon adjustment for BMI [1.03 (95% CI 0.96, 1.10); $P = 0.44$] [5]. Under the principles of Mendelian randomization [6], these findings provide strong evidence for greater adiposity being causally related to Type 2 diabetes risk. Given this evidence, we believe our paper provides a robust estimate of the burden of Type 2 diabetes related to being overweight [7].

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Professor David J. Hole, an author on the original paper, sadly passed away after submission of our original paper and therefore could not contribute to this letter.

Competing interests

None to declare.

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Weight gain may contribute to increased fracture risk in women treated with rosiglitazone

There is emerging evidence that the peroxisome proliferator-activated receptor-gamma activators, the thiazolidinediones (TZDs), might have adverse effects on bone. In mice, TZDs suppress bone formation [1] and in oestrogen-deprived rats they increase bone marrow adipogenesis and bone resorption [2]. In older diabetic women, TZDs are associated with a small loss of bone [3]. In the recent ADOPT study [4], long-term treatment of diabetic women with rosiglitazone was associated with increased limb fractures compared with those receiving other oral glucose-lowering treatments. Rosiglitazone was also associated with greater weight gain (7.7 kg compared with metformin).

In a previous population-based study of women, we found a positive independent association between body weight and risk of fracture [5], which led us to hypothesize that the increase in fractures seen in the TZD arm of the ADOPT study might be related to weight gain. In 1284 women [median age 59.4 years, interquartile range (IQR) 44.5–73.6], randomly selected for the Geelong Osteoporosis Study, 112 radiologically confirmed incident limb fractures (12 humerus, 34 forearm/wrist, five carpal/metacarpal, 30 proximal femur, three femoral shaft, three patella, five tibia/fibula, 13 ankle, seven tarsal/metatarsal) occurred over a median period of 6.4 years (IQR 5.2–7.4). Hazard ratio (HR) for fracture (Cox proportional hazards model predicting time to first limb fracture, age-adjusted), showed no association with baseline weight. However, after controlling for bone mineral density (BMD), HR for fracture increased 2% for each kg increase in weight, whether fractures were grouped or analysed as lower or upper limb (Table 1). Results were similar when based on fewer fractures ($n = 68$) for age 30–75 years, matching the ADOPT study population [4].

Our data show an association between increased weight and limb fracture in a random sample of women, median age 59.4 years, which is independent of BMD. Although the increased fracture rate in women taking rosiglitazone [4] could be due to adverse effects on bone, it may be partly explained by weight gain.

