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Unstable bodyweight and incident type 2 diabetes mellitus: A meta-analysis

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ABSTRACT

Aims/Introduction: The present meta-analysis aimed to clarify the association of unstable bodyweight with the risk of type 2 diabetes mellitus, an association that has been controversial among longitudinal studies.

Materials and Methods: An electronic literature search using EMBASE and MEDLINE was followed up to 31 August 2016. The relative risks (RRs) of type 2 diabetes mellitus in individuals with unstable bodyweight were pooled using the inverse variance method.

Results: Eight studies were eligible for the meta-analysis. The median duration of measurements of weight change and follow-up years for ascertaining type 2 diabetes mellitus were 13.5 and 9.4 years, respectively. The pooled RR for the least vs most stable category was 1.33 (95% confidence interval 1.12–1.57). Between-study heterogeneity was statistically significant ($P = 0.048$). Whether type 2 diabetes mellitus was ascertained by blood testing explained 66.0% of the variance in the logarithm of RR ($P = 0.02$). In three studies in which blood testing was carried out, type 2 diabetes mellitus risk was not significant (RR 1.06, 95% confidence interval 0.91–1.25). Furthermore, publication bias that inflated type 2 diabetes mellitus risk was statistically detected by Egger's test ($P = 0.09$).

Conclusions: Unstable bodyweight might be modestly associated with the elevated risk of type 2 diabetes mellitus; although serious biases, such as diagnostic suspicion bias and publication bias, made it difficult to assess this association.

INTRODUCTION

The incidence of type 2 diabetes mellitus is increasing with the prevalence of obesity. Bodyweight history provides information on type 2 diabetes mellitus risk beyond obesity, although obesity is an established risk factor for the development of type 2 diabetes mellitus[1]. For example, weight gain in adulthood, as well as obesity, elevates the risk of type 2 diabetes mellitus[2].

Weight cycling is hypothesized to elevate type 2 diabetes mellitus risk on the basis of both epidemiological findings and findings from animal studies. From the perspective of animal studies, weight cycling enhanced the adaptive immune response in adipose tissue, such as through increases in CD4(+) and CD8(+) T cells, and elevation in the expression of multiple T helper 1-associated cytokines[3]. The accumulation of these pro-inflammatory immune cells could contribute to the development of obesity-associated disorders, including type 2 diabetes mellitus. Another study showed that female rats that experienced weight cycling had higher blood insulin concentrations than those that did not[4]. Epidemiologically, one study[5] reported a positive correlation between weight variability and the risk of incident type 2 diabetes mellitus. However, results from further epidemiological studies that tested this hypothesis have not been consistent. The present meta-analysis aimed to clarify whether there is an association between unstable bodyweight and type 2 diabetes mellitus risk.

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METHODS

Study selection

Electronic literature searches using EMBASE and MEDLINE (from 1950 to 31 August 2016) were carried out for longitudinal studies that investigated the association between unstable

bodyweight (i.e., episodes of weight regain, weight cycling or weight fluctuation) and incident type 2 diabetes mellitus. Details of study keywords are shown in Appendix S1. Inclusion criteria were as follows: (i) studies that prospectively followed up incident type 2 diabetes mellitus; (ii) no participants were diagnosed with or reported to have type 2 diabetes mellitus at baseline; (iii) the period when weight change was examined preceded the period when type 2 diabetes mellitus was ascertained; and (iv) data on relative risks (RRs) for type 2 diabetes mellitus based on categorical variables in weight variability (episodes of weight regain, weight cycling or weight fluctuation) were presented, and standard errors (SEs) that corresponded to these RRs could be estimated.

In addition to these criteria, included studies must have adjusted the RR for type 2 diabetes mellitus for body mass index (BMI) or bodyweight considering the correlation between adiposity and frequency of weight cycling[6]. We contacted the authors of the three studies[7–9] that showed RRs that were not adjusted for BMI or bodyweight, and asked for information on the adjusted RRs if they had been estimated. The authors of two studies[7,9] did not respond to our request, and the author of the third study[8] responded that the additional data could not be provided because the database no longer existed. One study[6] did not analyze an episode of weight cycling as a dichotomous variable while the number of experiences of weight cycling was used as a continuous variable. The author of that study presented datum on the RR of type 2 diabetes mellitus for experiencing weight cycling at least once compared with no experience of weight cycling. However, we had to exclude that study, because the RR was not adjusted for BMI or bodyweight.

Data extraction

Two authors (SK and HS) extracted the following information relevant to study characteristics as well as several RRs with their corresponding SEs: the period when weight change was examined (i.e., examining weight change before the recruitment of participants or after recruitment), mean age, proportion of men and women, mean BMI, number of participants and cases, duration of measurements of weight change, follow-up years after ascertaining type 2 diabetes mellitus, percentage of lost-to-follow up participants, methods for obtaining information on weight change and incident type 2 diabetes mellitus, definition of unstable bodyweight, and confounders for which the RR of type 2 diabetes mellitus was adjusted. Inconsistencies were solved by discussion. If a study provided several RRs, the most completely adjusted RR was chosen.

Study quality was assessed by modifying the Newcastle Ottawa Quality Assessment Scale[10], so that it was applicable to our theme (Appendix S2). In summary, the Newcastle Ottawa Quality Assessment Scale consists of three major items: S (selection: 3 questions), C (comparability; 2 questions) and O (outcome: 3 questions). For each question that a study could answer with 'yes,' 1 point was awarded.

Data synthesis

To assess the risk of type 2 diabetes mellitus in relation to unstable bodyweight, the RRs for the least stable category compared with the most stable category were pooled using the inverse variance method, where the result from a random-effects model was chosen if between-study heterogeneity assessed by I^2 was statistically significant[11]. Otherwise a fixed-effects model was chosen. In order to identify potential sources of heterogeneity, analyses were stratified by pre-specified key study characteristics.

For studies that categorized participants into several categories based on a weight fluctuation index (FI-weight), we estimated the RR for an increment (1 kg) in the FI-weight and pooled it. FI-weight is a common indicator of weight variability that is calculated as the standard deviation of residuals around the regression line for weight with time. To estimate the RR for an increment of FI-weight, the logarithms of RR in several categories in an individual study were regressed on their corresponding mean FI-weight. This regression is called generalized least squares for trend estimation[12]. The program for estimating the RR for an increment was developed by Orsini *et al.*[13]

If the FI-weight in each category was presented as a range, we used the midpoint value of the upper and lower boundaries for intermediate categories. For the highest and lowest categories, we regressed the midpoint value of FI-weight on its corresponding *Z*-value for the rank percentile in the median of the upper and lower boundaries in each intermediate category, and extrapolated the regression line into the highest and lowest categories, assuming that the FI-weight was normally distributed. One study[14] presented the mean $(\bar{m})$ of FI-weight and its standard deviation in place of the mean or range of FI-weight in each category. In this case, we estimated the mean FI-weight using the following formula: $X_i = Z_i \times SD + \bar{m}$ where X_i and Z_i were the mean FI-weight and its corresponding median *Z*-value in each category, respectively.

Publication bias was assessed by two formal tests, the Begg's rank correlation test[15] and Egger's regression asymmetry test[16], as well as by visual inspection of a funnel plot. If publication bias was statistically detected, we adjusted the pooled RR for publication bias using the trim-fill method[17]. This method includes (i) the assumption that the funnel plot is symmetrical if there is no publication bias; (ii) detection of the hypothetically unpublished data causing the funnel plot to be asymmetrical; and (iii) recalculation of the pooled RR after filling these data as if they had actually existed. Two-sided $P < 0.05$ were considered statistically significant except for the test of publication bias in which the level of significance was $P < 0.10$[18]. All analyses were based on statistical software Stata version 12 (StataCorp, College Station, Texas, USA).

RESULTS

Study characteristics

Of 719 articles retrieved from the electronic literature searches, eight studies[14,19–25] met our inclusion criteria (Figure 1). The

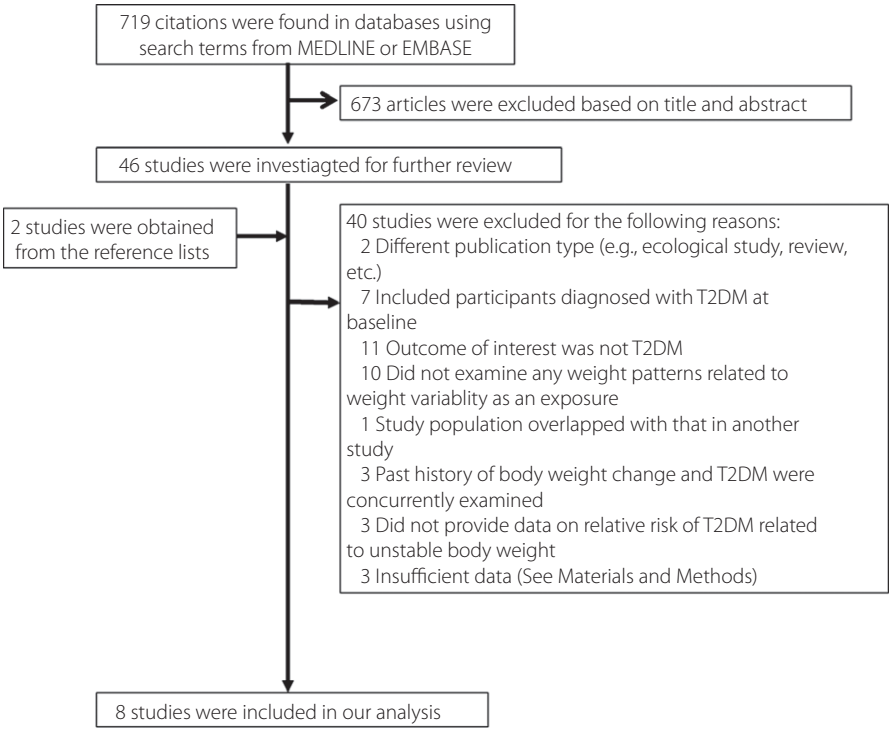

Figure 1 | Flow chart of literature search for eligible studies. T2DM, type 2 diabetes mellitus

characteristics of the eight included studies are given in Table 1. Four studies[14,19,21,23] examined weight change before enrollment of the participants, whereas four studies[20,22,24,25] examined weight change after enrollment. The duration of measurements of weight change ranged from 3 to 32 years (median 13.5 years). Median follow-up duration for investigating incident type 2 diabetes mellitus was 9.4 years. One study[24] investigated incident type 2 diabetes mellitus only once, whereas there were follow-up periods ranging from 3 to 24 years in the remaining seven studies. Four studies[19–22] had no participants lost to follow up. Three studies[14,21,23] and one study[20] recruited only women and men, respectively. None of the remaining four studies[19,22,24,25] that included both men and women analyzed each sex separately.

To obtain information on weight change, four studies[19,21–23] used a questionnaire, whereas the researcher measured bodyweight in the other four studies[20,22,24,25]. In three studies[19,22,24], laboratory screening (i.e., blood testing) was carried out for participants who did not report that they had diabetes to confirm the presence or absence of diabetes, whereas the other five studies substituted other methods, such as a questionnaire, self-report and various records of blood testing.

Table 2 shows the indicators of weight variability used in each included study, and definitions of the most and least stable categories in terms of weight variability. Four studies[19,21,22,25] used episodes of weight cycling or weight regain to show weight variability, and three studies[14,20,24] used weight fluctuation. One study[22] examined weight variability from two perspectives: episodes of weight cycling and weight fluctuation. Only one study[21] defined intentional weight loss as weight loss followed by weight regain.

The results of scoring of study quality are shown in Appendix S2. The mean study score was 4.9 (standard deviation 1.6; range 0–8) according to the modified Newcastle Ottawa Quality Assessment Scale (Appendix S2). While four studies[14,23–25] recruited participants from the general population, the remaining four studies recruited participants from specified populations, such as those with obesity or an excess BMI (two studies[22,24]), nurses (one study[21]) and smokers (one study[20]). One study[24] did not confirm that all participants did not have diabetes at baseline.

Overall analysis of type 2 diabetes mellitus risk in relation to unstable weight

Overall RR (95% CI) of type 2 diabetes mellitus in the least stable weight category compared with the most stable weight category was 1.33 (95% confidence interval [CI]: 1.12–1.58; Figure 2). Between-study heterogeneity was significant (I^2 = 50.7%, P = 0.048). When the RR for the highest vs the lowest category of weight fluctuation was chosen to replace that for episodes of weight cycling in the study by French *et al.*[23], the overall RR was 1.23 (95% CI: 1.11–1.37). The risk of type 2 diabetes mellitus for an increment in FI-weight could be estimated in four studies[14,20,23,24]. The pooled RR for a 1-kg

Table 1 | Study characteristics of eight studies selected for the meta-analysis

Author	Period weight change[†]	Age[‡] (years)	Men (%)	BMI[‡] (kg/m^2)	No. participants	No. cases	Duration weight[§] (years)	Type 2 diabetes mellitus[§] (years)	Lost to follow up(%)	Methods weight[¶]	DM[¶]	Covariates
Hanson[24]	After	49	38	29	584	162	6	††	††	M	B	Age, sex, smoking, BMI, weight gain
French[23]	Before	55–69	0	27	30,290[‡‡]	914	32	6	17%	Q	S	Age, (sex), smoking, PA, BMI, BMI^2, education,marriage, hormone use
Brancati[14]	Before	50	0	24[§§]	916	35	30	16	13%	Q	R/S	Age, (sex), smoking, PA, FH of DM, BMI
Moore[22]	After	30–50	54	29	458	70	16	17	0%	M	R/B	Age, sex, smoking, PA, alcohol, BMI, height, education
Field[21]	Before	39	0	25	37,173	258	4	3	0%	Q	S	Age, (sex), PA, alcohol, magnesium intake, total intake, BMI
Kataja-Tuomola[20]	After	57	100	26	20,952	535	3	7	0%	M	R	Age, (sex), smoking, alcohol, BP, BMI, TC, HDL
Waring[19]	Before	50	45	¶¶	1,476	217	10	24	0%	M	B	(Age), sex, smoking, alcohol, obesity status(based on BMI), education, hormone use (women)
Neamat-Allah[25]	After	50	42	27.3[†††]	35,270	399	7.2	2.5	22	Q	R/S	(Age), sex, smoking, alcohol, obesity status(based on BMI), education, hormone use (women)

[†]Period of examination of weight change (i.e., examining weight change before the recruitment of participants or after recruitment). [‡]A value at enrollment of participants. [§]Duration during which bodyweight and ascertainment of type 2 diabetes mellitus were examined. [¶]Methods for collecting data on weight change and ascertainment of type 2 diabetes mellitus. [††]No follow-up period for ascertainment of type 2 diabetes mellitus (i.e., type 2 diabetes mellitus was screened only once). [‡‡]Number of participants analyzed for diabetes risk in relation to weight variability was 30,242. [§§]Values at 5 years before the enrollment of participants. [¶¶]A total of 51% of participants had a body mass index (BMI) of ≥25 kg/m^2. [†††]Derived from another study by Haftenberger *et al.*[31], which had the same cohort as the included study. B, blood test; BMI, body mass index; BP, blood pressure; FH, family history; HDL, high density lipoprotein; Mg, magnesium; No., number of; PA, physical activity; Q, questionnaire; R, record including medical record, registry, and death certificates; S, self-report; TC, total cholesterol; vari, variability; WHR, waist-hip ratio.

increment in FI-weight was 1.15 (95% CI: 1.02–1.30; Figure 3). Between-study heterogeneity was significant (I^2 = 79.6%, P = 0.005).

Sensitivity analysis of type 2 diabetes mellitus risk for the least stable vs the most stable weight category

Except for one study[21] that discriminated intentional weight loss followed by weight regain from unintentional weight loss, the pooled RR was 1.32 (95% CI: 1.09–1.60), which was not different from the overall RR (P = 0.88). Table 3 shows the stratified analyses of type 2 diabetes mellitus risk according to several study characteristics. Most of the stratified analyses did not modify type 2 diabetes mellitus risk. For example, in studies using episodes of weight cycling or weight regain to show weight variability, the pooled RR of type 2 diabetes mellitus for the least vs the most stable category was 1.32 (95% CI: 1.13–1.54), which was only slightly different from the pooled RR (1.41, 95% CI: 0.93–2.14) in studies using weight fluctuation. There was not a significant difference (P = 0.22) between the pooled RR of six studies that adjusted the RR for five or more

Table 2 | Indicators of weight variability and definition of unstable bodyweight

Author	Indicator	Category	
		Least stable	Most stable (referent)
Hanson[24]	Fluctuation	Median of upper half of weight fluctuation	Median of lower half of weight fluctuation
French[23]	Episode†	Reported both weight loss and gain of ≥10% of initial weight	Reported weight change within 5% of initial weight
	Fluctuation	Highest quartile of weight fluctuation	Lowest quartile of weight fluctuation
Brancati[14]	Fluctuation	Highest quartile of weight fluctuation	Lowest quartile of weight fluctuation
Moore[22]	Episode	Experienced ≥17.8 kg of weight loss during the first 8 years and regained lost weight during the next 8 years	Sustained weight within 2.25 kg/year during both the first and the next 8 years
Field[21]	Episode	Reported ≥9.1 kg of intentional weight loss at least 3 times	Reported ≥4.5 kg of intentional weight loss <3 times
Kataja-Tuomola[20]	Fluctuation	Highest quintile of weight fluctuation	Lowest quintile of weight fluctuation
Waring[19]	Episode	Experienced weight cycling of ≥1 kg/m^2 at least once	Not experiencing weight cycling of ≥1 kg/m^2
Neamat-Allah[25]	Episode	Experienced weight cycling of ≥1 kg/m^2 at least once	Not experiencing weight cycling of ≥1 kg/m^2

†Episode of weight cycling or weight regain.

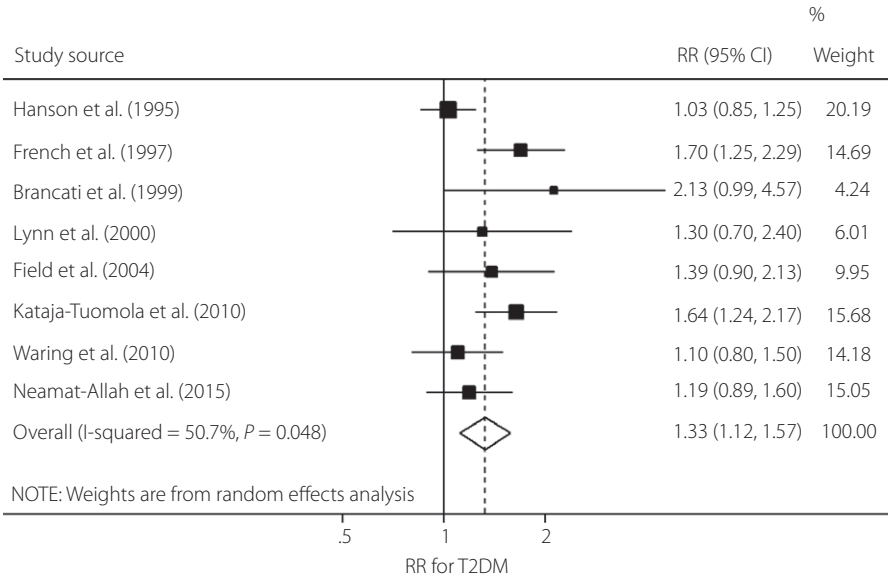

Figure 2 | Forest plot of relative risk (RR) with 95% confidence interval (CI) of type 2 diabetes mellitus (T2DM) for the least stable category compared with the most stable category in terms of weight variability. Horizontal lines indicate the range of 95% CI. Areas of the square are proportional to the study weight expressed as the inverse of the square of standard error based on a random-effects model.

of the eight potential confounders (age, sex, smoking, alcohol, physical activity, family history of diabetes mellitus, educational background and blood pressure), as well as BMI or bodyweight (RR 1.41, 95% CI: 1.22–1.62) and that of the remaining two studies that did not (RR 1.08, 95% CI: 0.91–1.29).

The pooled RR of type 2 diabetes mellitus was significant both in studies that recruited women only (RR 1.63, 95% CI: 1.29–2.07) and in other studies that included men only (RR 1.18, 95% CI: 1.05–1.34). In addition, in two studies that exclusively recruited participants with obesity or excess BMI[22,24], the pooled RR for type 2 diabetes mellitus was not significant (RR 1.05, recruited 0.88–1.26), whereas in the other studies that included non-obese participants, the pooled RR was 1.41 (95% CI: 1.23–1.62). However the difference was not significant (P = 0.13).

Examination of the methods for obtaining information on weight change did not modify the pooled RR for type 2 diabetes mellitus (P = 0.33), although it was modified by methods

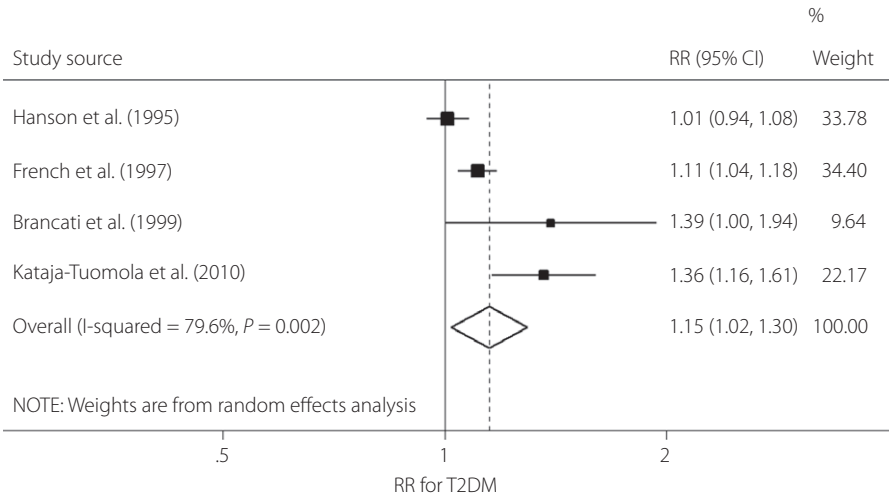

Figure 3 | Forest plot of relative risk (RR) with 95% confidence interval (CI) of type 2 diabetes mellitus (T2DM) in relation to a 1 kg increment in a weight fluctuation index of bodyweight variability. The RRs in each study and the overall RR are indicated by circles and diamonds, respectively. Horizontal lines indicate the range of 95% CI. Areas of the square are proportional to the study weight expressed as the inverse of the square of standard error based on a random-effects model.

Table 3 | Stratified analyses of the type 2 diabetes mellitus risk for the least stable category vs the most stable category in terms of weight variation based on the definitions described in Table 2

Variable	*n* data	RR (95% CI)	Q- statistics	I^2	*P*-value for heterogeneity	*Meta regression
Total participants limited to those with obesity or overweight	8	1.33 (1.12–1.57)	14.2	50.7%	0.048	–
Yes	2	1.05 (0.88–1.26)	0.5	0.0%	0.48	0.13
No	6	1.41 (1.23–1.62)	7.3	31.8%	0.20	
Sex						
Women only	3	1.63 (1.29–2.07)	1.1	0.0%	0.58	0.13
Including men	5	1.18 (1.05–1.34)	7.5	46.8%	0.11	
Indicator of weight instability						
History of weight cycling or regaining weight	5	1.32 (1.13–1.54)	4.5	10.1%	0.35	0.91
Weight fluctuation	3	1.41 (0.93–2.14)	9.3	78.5%	0.01	
Methods for obtaining information on weight change						
Questionnaire	4	1.45 (1.20–1.74)	3.7	19.6%	0.29	0.33
Confirmation by measurement	4	1.18 (1.03–1.36)	7.5	60.0%	0.06	
Methods for ascertaining Type 2 diabetes mellitus						
Including blood test	3	1.06 (0.91–1.25)	0.6	0.0%	0.76	0.02
Self-report or registry only	5	1.50 (1.29–1.75)	4.3	6.6%	0.37	
No. confounders for which the risk measure was adjusted						
<5	2	1.08 (0.91–1.29)	1.5	34.2%	0.22	0.22
≥5	6	1.41 (1.22–1.62)	7.4	32.4%	0.19	
Duration of assessing weight change						
<10 years	4	1.27 (1.01–1.59)	7.6	60.6%	0.06	0.54
≥10 years	4	1.43 (1.08–1.90)	5.0	40.5%	0.17	
Follow-up duration for ascertaining Type 2 diabetes mellitus						
<10 years	5	1.28 (1.13–1.45)	11.6	65.5%	0.02	0.87
≥10 years	3	1.27 (0.92–1.76)	2.5	20.4%	0.29	

**P* for comparison of the mean difference across strata. CI, confidence interval; RR, relative risk.

for ascertaining type 2 diabetes mellitus. Whether or not blood testing was carried out in participants who did not report that they had diabetes significantly explained 66.0% of the variance in logarithms of RR for type 2 diabetes mellitus ($P = 0.02$). In three studies in which blood testing was carried out, the pooled RR for type 2 diabetes mellitus was not significant (RR 1.06,

95% CI: 0.91–1.25), but in the remaining five studies in which blood testing was not carried out, the pooled RR was 1.50 (95% CI: 1.29–1.75).

Publication bias

Figure 4 is a funnel plot in which logarithms of RR for type 2 diabetes mellitus for the least stable category compared with the most stable category of bodyweight are plotted against their corresponding SEs. The asymmetry of the funnel plot suggested that publication bias inflated type 2 diabetes mellitus risk, which was statistically supported not by Begg's test ($P = 0.46$), but by Egger's test ($P = 0.09$). Adjustment for publication bias using the trim and fill method attenuated the type 2 diabetes mellitus risk (RR 1.23, 95% CI: 1.03–1.47). Publication bias was not indicated for the pooled RR for a 1-kg increment in FI-weight ($P = 0.50$ for Begg's test; $P = 0.72$ for Egger's test).

DISCUSSION

The current meta-analysis showed that the pooled RR for type 2 diabetes mellitus associated with unstable bodyweight was significant, which suggested the need for frequent monitoring of bodyweight to minimize its variability. In this meta-analysis, all RRs were adjusted for BMI or bodyweight. Therefore, the positive association of unstable bodyweight with the risk of type 2 diabetes mellitus was independent of the association of excess bodyweight with future type 2 diabetes mellitus. However, the magnitude of type 2 diabetes mellitus risk associated with unstable bodyweight was much smaller than that with being overweight (RR 2.99) or obese (RR 7.19)[1]. This finding from the present meta-analysis does not influence the clinical recommendation that everyone should make an effort to maintain normal weight.

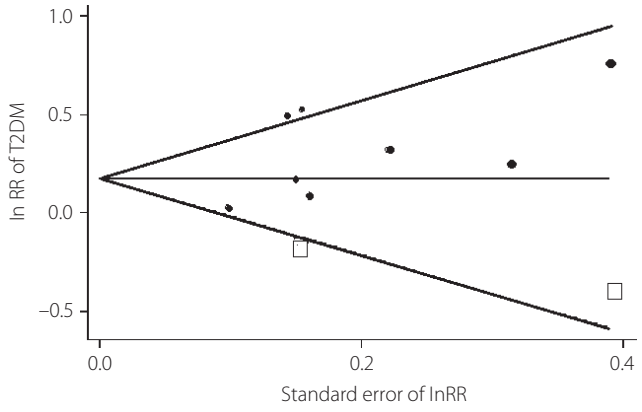

Figure 4 | Funnel plot of relative risk (logarithms of relative risk [lnRR]) of type 2 diabetes mellitus (T2DM) for the least stable category compared with the most stable category of bodyweight in relation to the standard error in the lnRR. The lnRR is plotted against the standard error of lnRR. The asymmetrical funnel plot suggested publication bias, which was supported by statistical testing (see Results). The pooled RR for T2DM would be attenuated if some hypothetical studies which, if they existed and were published, could reconstruct the asymmetry of the funnel plot were added to the genuine studies indicated by circles in order to adjust for the pooled RR for publication bias.

One possible explanation for this finding is that weight cycling promotes abdominal adiposity linked to insulin resistance. This explanation is supported by the study showing that overweight individuals with a history of weight cycling had significantly more fat on the upper body than overweight controls[26]. Another possible explanation is the existence of a threshold in BMI above which type 2 diabetes mellitus risk is elevated; individuals with large weight fluctuations will have a longer duration of excess BMI than those with small weight fluctuations, even if the average BMI throughout the time-period examined were the same. This explanation is supported by studies reporting a positive association between the duration of obesity and incident type 2 diabetes mellitus[27,28].

Serious biases should be addressed in the present meta-analysis. First, publication bias that overestimated type 2 diabetes mellitus risk in relation to unstable bodyweight was suggested. Even though adjustment for publication bias using the trim-fill method did not change the significance of the type 2 diabetes mellitus risk, the impact of unpublished studies showing a non-significant association between unstable bodyweight and type 2 diabetes mellitus risk would not be completely predictable. Second, the pooled RR was lower in studies in which blood testing was carried out to ascertain incident diabetes mellitus compared with studies that did not carry out blood testing. It was suggested that more type 2 diabetes mellitus cases had been overlooked among weight-cyclers than among non-weight-cyclers. Weight-cyclers would be more concerned about diabetes and would undergo more frequent blood testing than non-weight cyclers. The type 2 diabetes mellitus risk could have been overestimated by diagnostic suspicion bias, which is defined as 'knowledge of the patient's prior exposure to a putative cause may influence both the intensity and the outcome of the diagnostic process'[29].

Several limitations should be addressed. First, most of the included studies did not discriminate intentional weight loss from unintentional weight loss. Two studies, which were excluded because of lack of adjustment for BMI or weight, reported type 2 diabetes mellitus risk for weight regain after intentional weight loss. However, the results of these studies were inconsistent. One study[9] showed that participants who succeeded in a 5% or greater weight loss had lowered their risk of type 2 diabetes mellitus compared with those who failed to lose weight, regardless of whether weight was regained or not. Another study[6] showed that type 2 diabetes mellitus risk was elevated according to the number of experiences of weight cycling. However, it was unclear whether weight-cyclers were compared with non weight-cyclers who maintained weight loss or those who neither lost nor gained weight. Further studies, including weight loss trials, are required to examine the effect

of weight regain after intentional weight loss on incident type 2 diabetes mellitus, the RR of which was adjusted for obesity and weight change.

Second, although the present meta-analysis adjusted the RR for obesity by providing one criterion that the RR be adjusted for BMI or bodyweight, it was impossible to adjust the RR for potentially important confounders, such as physical activity, family history of diabetes and blood pressure, as well as obesity, because the confounders for which the RR of type 2 diabetes mellitus was adjusted were too heterogeneous among studies. The stratified analysis did not indicate that the number of confounders used for the risk assessment modified the magnitude of type 2 diabetes mellitus risk. Nevertheless, insufficient adjustment could bias the results. Third, there is the potential of errors in recalling bodyweight, although the reliability of self-report was generally acceptable[30]. Fourth, the definition of unstable bodyweight varied among studies, which could cause a misclassification bias. In particular, using FI-weight as an indicator of weight variability could have resulted in overlooking a maximum or minimum weight, which would lead to underestimation of weight variability.

In conclusion, unstable bodyweight might be modestly associated with the risk of type 2 diabetes mellitus, although serious biases made it difficult to assess this association. This finding suggested the need for frequent monitoring of bodyweight to minimize its variability. Further studies that include weight loss trials as well as observational studies are required to examine the association of weight regain after intentional weight loss with type 2 diabetes mellitus risk.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendi S1 | Search strategy of this meta-analysis using study keywords.
Appendix S2 | Study quality of the eight selected studies determined by the modified Newcastle Ottawa Quality Assessment Scale.