



# Association between weight cycling and risk of developing diabetes in adults: A systematic review and meta-analysis

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## Keywords

Body-weight fluctuation, Diabetes, Weight cycling

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## ABSTRACT

**Aims/Introduction:** In this meta-analysis, we aimed to explore the association between bodyweight cycling (weight fluctuation) and the risk of developing diabetes.

**Materials and Methods:** We analyzed data from eligible cohort studies that assessed the association between weight cycling in adults and the risk of developing diabetes from online databases PubMed, Cochrane Library and EMBASE databases (1966 to April 2020). We pooled data using relative risks (RRs) with a random effects model.

**Results:** A total of 14 studies involving 253,766 participants, including 8,904 diabetes events, were included. One study included eight independent reports, resulting in 21 reports in 14 studies. Summary analysis showed that individuals who suffered weight cycling had a higher risk of diabetes (RR 1.23, 95% confidence interval 1.07–1.41;  $P = 0.003$ ). However, the association between weight cycling and the risk of developing diabetes was not observed in obese participants (body mass index  $\geq 30$  kg/m<sup>2</sup>;  $P = 0.08$ ).

**Conclusions:** The present meta-analysis showed that weight cycling was a strong independent predictor of new-onset diabetes. Future studies are required to detect the causal links between weight cycling and the risk of developing diabetes.

## INTRODUCTION

Obesity is increasing worldwide<sup>1</sup>. In 2015, a total of 711.4 million people were obese, and overweight or obesity contributed to 4.0 million deaths in 1 year alone<sup>2</sup>. Obesity is an independent risk factor for diabetes<sup>3</sup>. Therefore, weight loss is widely advised by physicians for obese patients, and it has been estimated that >30 million people in the USA are overweight and in a battle to lose weight<sup>4</sup>. However, the success rate is not impressive on account of multiple factors, such as genetic predisposition, emotions and barriers in a person's social or cultural environment<sup>5,6</sup>. According to the Nurses' Health Study II (NHSII), just <10% of the women who lost weight successfully were able to maintain their loss of weight<sup>7</sup>. Repeated weight loss followed by weight gain caused weight fluctuation or weight cycling. The National Task Force on the Prevention and Treatment of Obesity summarized in reports weight cycling

from 1966 to 1994 carried out in normal weight, overweight and obese individuals. They concluded that the available evidence regarding increased morbidity as a result of weight cycling is not sufficiently compelling to override the potential benefits of moderate weight loss<sup>8</sup>. Since 1994, numerous studies investigating weight cycling have been carried out and have yielded controversial results<sup>9–17</sup>. Therefore, we undertook the present meta-analysis based on available evidence from published cohort studies to establish whether participants with weight cycling had a higher risk of diabetes.

## METHODS

The present meta-analysis was prospectively registered with PROSPERO International Prospective Register of Systematic Reviews (PROSPERO identifier CRD42018110985). We carried out this meta-analysis of studies assessing the association between weight cycling and the risk of developing diabetes according to the Conducting Systematic Reviews and Meta-

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Analyses of Observational Studies of Etiology (COSMOS-E) Guidelines<sup>18</sup>.

### Search strategy and selection criteria

PubMed, EMBASE databases and the Cochrane library were searched from 1966 to 24 September 2018. Then, hand-searching was undertaken according to references from these relevant papers. The search was subsequently updated to 7 April 2020. One newly identified study was included in the analyses<sup>19</sup>. The search strategies are shown in Appendix S1.

Our analyses included cohort studies if they had published relative risk (RR) estimates with 95% confidence intervals (CI) of the association between weight cycling and the risk of developing diabetes in populations free of diabetes at baseline aged  $\geq 18$  years. As no single definition and measurement are currently endorsed, we defined weight cycling as weight gain or loss in a specific period, and change in the opposite direction (loss or gain) in the next period. Detailed descriptions for definitions and measurements of weight cycling in different studies are shown in Table S1. The primary outcome was new-onset diabetes. If multiple publications from the same cohort study were reviewed, we included the publication with the longest follow-up period.

### Statistical analysis

We assessed pooled data using RRs with a random effects model, and any results in studies that were stratified by sex were treated as two separate reports<sup>20</sup>. Weight cycling was measured in two different ways; that is, weight cycles as categorical variables (such as weight loss and gain or gain and loss  $\geq 2.27$  kg<sup>9</sup>, 4.54 kg<sup>10</sup> or  $\geq 1.125$  kg/year<sup>11</sup>) and deviation degree of weight as continuous variables (such as root mean square error<sup>21</sup>, coefficient of variation<sup>22</sup>, body mass index [BMI] variability or average successive variability of weight<sup>17</sup>). All RRs for outcomes were transformed as categorical variables (details are shown in Appendix S2).

The modified Newcastle–Ottawa scale (NOS) was used for grading the quality of cohort studies (Appendix S2)<sup>23</sup>. Publication bias was assessed using funnel plots, and Egger's and Begg's tests<sup>24,25</sup>. The sensitivity analyses were carried out at the levels of both report and study to assess the effect of each report or each study on the overall findings. For the report level of analysis, we omitted one report at a time from the analyses and summarized the RR of the remaining reports. For the study level of analysis, we omitted one study, which might include several reports, at each time and summarized the RR of the remaining studies. We estimated heterogeneity among studies with the  $I^2$  statistic<sup>26</sup>, and used meta-regression to assess the contribution to heterogeneity of sex, age, location, number of participants, percentage of events, follow-up duration, study quality, original measurement of weight cycling, method for weight ascertainment, follow-up rate and duration of assessing weight change. In the meta-regression, variables in the univariable analyses with  $P$ -values  $< 0.1$  were considered statistically

significant and were then included in the multivariable models, and an overall  $P$ -value  $< 0.05$  was considered statistically significant in the multivariable regression analysis<sup>27,28</sup>. We undertook subgroup analyses based on sex (male, female or both), age ( $\leq 60$  or  $> 60$  years), location (North America, Europe or Asia), follow-up duration ( $> 10$  or  $\leq 10$  years), study quality (NOS score  $> 7$  or  $\leq 7$ ), original measurement of weight cycling (deviation degree or weight cycle), method of weight ascertainment (self-reported or measured at each visit), intentional or unintentional weight cycling, BMI (BMI  $< 25$  kg/m<sup>2</sup>, 25 kg/m<sup>2</sup>  $\leq$  BMI  $< 30$  kg/m<sup>2</sup> or BMI  $\geq 30$  kg/m<sup>2</sup>) and follow-up rate ( $> 80\%$  or  $\leq 80\%$ ).

Data were analyzed with Stata statistical software version 12.0 (StataCorp, College Station, TX, USA), and all statistical tests were two-sided with a significance level of 0.05.

## RESULTS

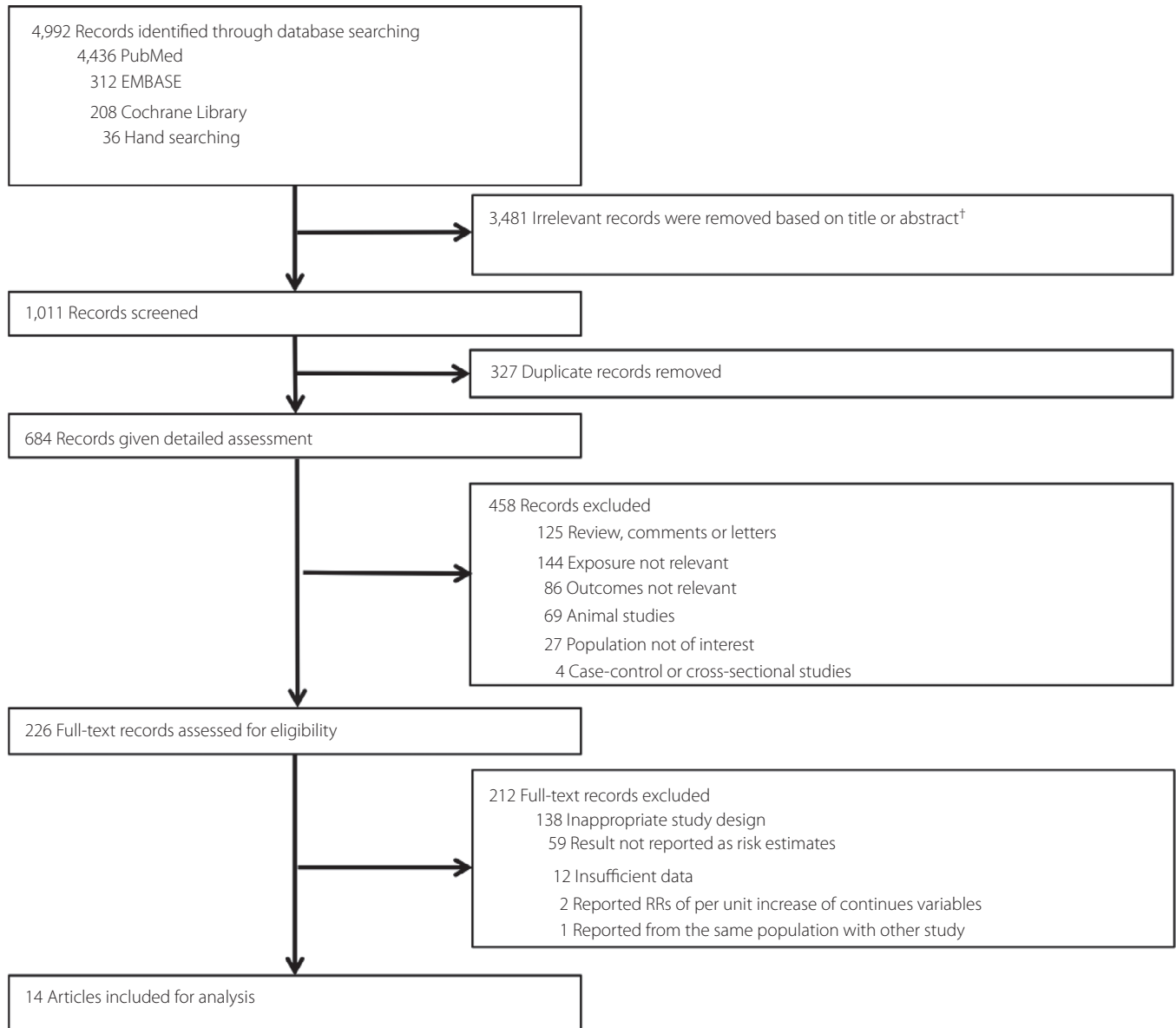
### Study selection and study characteristics

After excluding 4,992 ineligible studies identified in the initial search, 14 cohort studies were eligible for the present study (Figure 1)<sup>9–14,16,17,19,29–33</sup>. Notably, two studies<sup>34,35</sup> were excluded because RRs of 1 kg average successive variability of weight or root mean square error increase were reported, and could not be transformed to categorical variables for further analysis. In addition, one publication<sup>36</sup> was excluded from our analysis because the participants came from the same study, and we included the article with a longer duration<sup>30</sup>.

In total, 14 studies with 253,766 individuals (8,904 new-onset diabetes) were included. The age of participants ranged from 20 to 75 years, and the majority of the participants were aged  $> 50$  years. The participants in six studies<sup>9,10,13,16,19,31</sup> had an average BMI  $\geq 25$  kg/m<sup>2</sup> ( $n = 119,517$ , 47.1%), participants in three studies<sup>12,17,29</sup> had an average BMI  $< 25$  kg/m<sup>2</sup> ( $n = 36,112$ , 14.2%) and the remaining studies<sup>11,14,30,32,33</sup> did not provide a BMI. Three studies involved weight cycling as a result of intentional weight loss, and the remaining studies could not be distinguished based on the available information. The median follow-up time of these cohort studies ranged from 2.5 to 32 years. Of the 14 publications, 12 were rated high quality ( $\geq 6.5$ ) based on the Newcastle–Ottawa scale score (Table S2). Yokomichi *et al.*<sup>12</sup> divided participants into groups of rural men, rural women, urban men and urban women. They then reported results as weight cycling end at weight loss and end at weight gain, respectively. Therefore, eight reports were generated and added to the other 13 studies, resulting in 21 reports in 14 studies.

### Weight cycling and risk of developing diabetes

The available evidence shows that weight cycling was significantly associated with the risk of developing diabetes (RR 1.23, 95% CI 1.07–1.41,  $P = 0.003$ ; Figure 2). The heterogeneity was evident among the studies ( $I^2 = 73.9\%$ ,  $P < 0.001$  for heterogeneity).



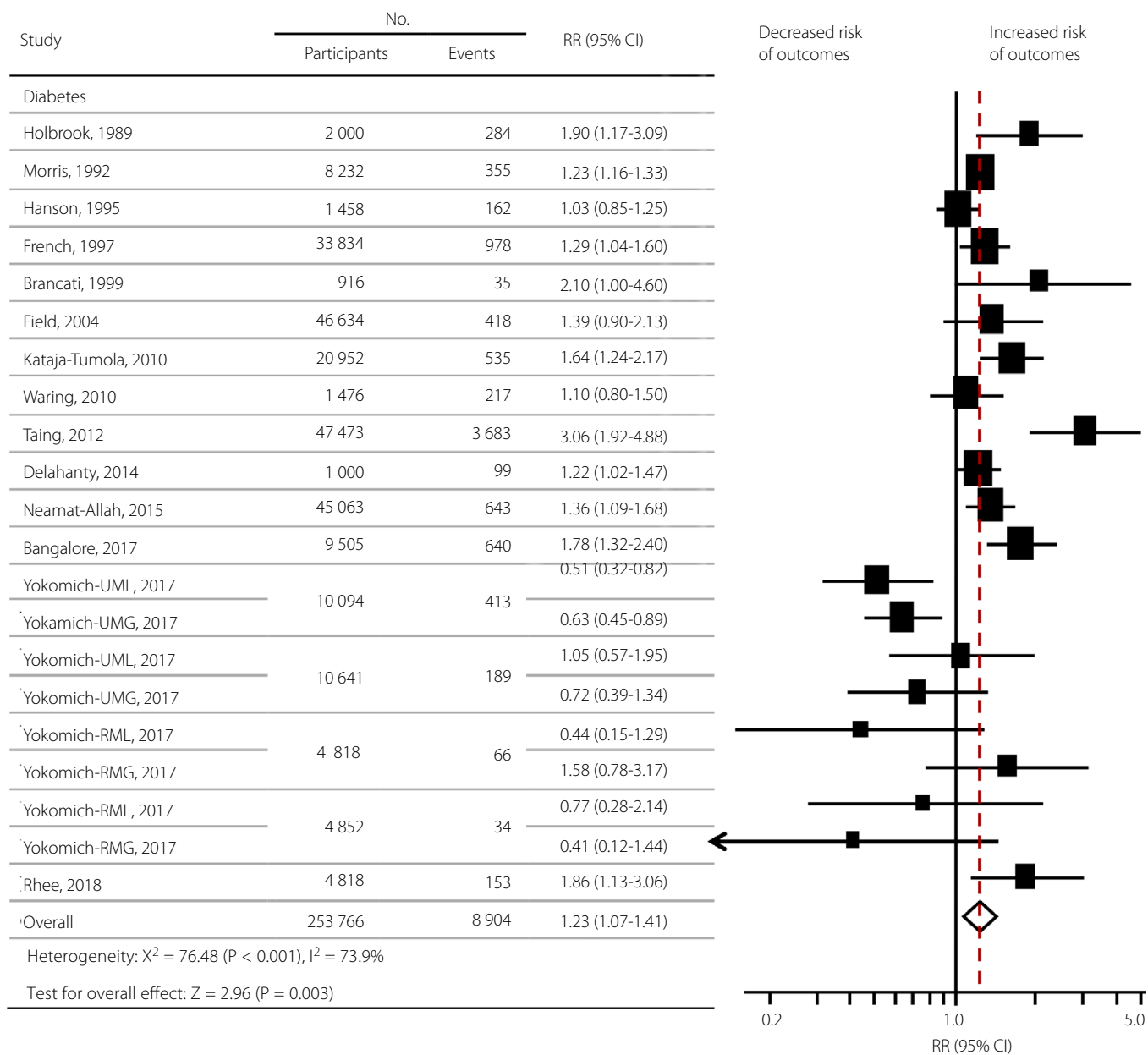
**Figure 1** | Flowchart of the study selection. †Exact reasons for exclusion were not documented. RRs, relative risks.

### Meta-regression

Significant heterogeneity ( $I^2 > 50\%$ ) was detected among these studies. Therefore, we undertook meta-regression analyses to assess the contribution to heterogeneity. The results suggested that the age of participants ( $P = 0.04$  in the univariable models), location ( $P = 0.02$  in the univariable models), follow-up duration ( $P = 0.01$  in the univariable models), study quality ( $P = 0.007$  in the univariable models), method of weight ascertainment ( $P = 0.01$  in the univariable models) and duration of the assessment of weight change ( $P = 0.01$  in the univariable models) were the major sources of heterogeneity of the studies (the overall  $P = 0.001$  in the multivariable models; Table S3).

### Sensitivity and subgroup analyses

The results of the sensitivity analyses showed that the observed association between weight cycling and the risk of developing diabetes was not altered after excluding any report (Figure S1) or study (Table S4). Furthermore, three of the 21 reports of diabetes involved intentional weight loss. The subgroup analyses of three reports showed that individuals with intentional weight cycling had a higher risk of diabetes ( $P < 0.001$ ; Table 1); however, the small number of studies limits the conclusion drawn based on these studies. Furthermore, the association was not detected in several subgroup analyses (Table 1), such as in participants aged  $\leq 60$  years ( $P = 0.16$ ), in studies using weight



**Figure 2** | Summary relative risks (RRs) of the association between weight cycling and diabetes. The size of data markers is proportional to the weight of each report. RRs and 95% confidence intervals (CI) were calculated using a random effects model to pool the data. Error bars indicate the 95% CIs. RR data are rounded to two decimal places; error bars reflect unrounded values. RMG, weight cycle in rural men ending at gain; RML, weight cycle in rural men ending at loss; RWG, weight cycle in rural women ending at gain; RWL, weight cycle in rural women ending at loss; UMG, weight cycle in urban men ending at gain; UML, weight cycle in urban men ending at loss; UWG, weight cycle in urban women at gain; UWL, weight cycle in urban women ending at loss.

cycle as the original measurement for cycling ( $P = 0.55$ ), participants with normal weight ( $P = 0.20$ ) or obesity ( $P = 0.55$ ). This might be due to the fact that null association for weight cycling and risk of developing diabetes was observed in eight reports from the Yokomichi *et al.*<sup>12</sup> study among 21 reports. Therefore, we also summarized the overall RR and carried out

the subgroup analyses after omission of the Yokomichi *et al.* study. The overall result after omitting the Yokomichi *et al.* study was consistent with the original findings of increased risk of diabetes with weight cycling (RR 1.41, 95% CI 1.25–1.59,  $P < 0.001$ ). The significance of the association between weight cycling and the risk of diabetes was detected in most subgroups

after omitting the Yokomichi *et al.* study ( $P < 0.05$ ; Table S5), such as in participants aged  $\leq 60$  years ( $P < 0.001$ ), in studies using weight cycle as the original measurement for cycling ( $P < 0.001$ ) and participants with normal weight ( $P = 0.002$ ). However, null association was still detected in obese individuals ( $BMI \geq 30 \text{ kg/m}^2$ ), even after removing the Yokomichi *et al.* study ( $P = 0.08$ ; Table S5).

**Publication bias**

Egger’s ( $P = 0.53$ ) and Begg’s ( $P = 0.81$ ) tests suggested that there was no significant publication bias. Visual inspection of the funnel plot is shown in Figure S2.

**DISCUSSION**

A total of 253,766 participants and 8,904 new-onset diabetes patients were included from the 14 studies in the pooled analysis. In general, individuals with weight cycling had a significant 23% increased risk of developing diabetes. The meta-regression provided the specific potential sources of heterogeneity, such as age, location, follow-up duration and method used for the weight ascertainment.

Although most large studies, such as the Rancho Bernardo cohort, Iowa Women’s Health Study and the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study<sup>14,19,31</sup> suggested that weight cycling is associated with the risk of developing

**Table 1** | Subgroup analyses for the association of weight cycling and the risk of diabetes

	Reports (n)	RR (95% CI)	$P_1$	$I^2$ (%)	$P_2$
All studies	21	1.23 (1.07–1.41)	0.003	73.9	<0.001
Sex					
Male	6	0.97 (0.57–1.66)	0.92	85.4	<0.001
Female	8	1.26 (0.99–1.60)	0.06	68.2	0.003
Both	7	1.34 (1.13–1.59)	0.001	61.8	0.015
Age (years)					
$\leq 60$	17	1.11 (0.96–1.28)	0.16	69.0	<0.001
$> 60$	4	1.84 (1.30–2.60)	0.001	75.5	0.007
Location					
North America	10	1.38 (1.19–1.59)	<0.001	69.2	0.001
Europe	2	1.46 (1.22–1.75)	<0.001	7.1	0.30
Asia	9	0.82 (0.57–1.18)	0.28	65.5	0.003
Follow-up duration (years)					
$\geq 10$	12	0.94 (0.74–1.21)	0.64	72.1	<0.001
$< 10$	9	1.50 (1.26–1.79)	<0.001	72.7	<0.001
Original measurement of weight fluctuation					
Deviations degree	7	1.38 (1.18–1.60)	<0.001	65.4	0.008
Weight cycle	14	1.08 (0.84–1.38)	0.55	77.3	<0.001
Study quality					
Score $> 7$	12	0.94 (0.77–1.16)	0.58	66.9	<0.001
Score $\leq 7$	9	1.59 (1.32–1.91)	<0.001	72.8	<0.001
Method for weight ascertainment					
Self-reported	5	1.61 (1.22–2.12)	0.001	67.4	0.17
Measured at each visit	8	1.33 (1.17–1.53)	<0.001	63.3	0.008
Missing information	8	0.72 (0.54–0.95)	0.019	32.8	0.17
Weight loss					
Intentional	3	1.23 (1.16–1.31)	<0.001	0.0	0.85
Unintentional	None				
No discrimination	18	1.21 (0.99–1.47)	0.069	77.7	<0.001
BMI at baseline ( $\text{kg/m}^2$ )					
$BMI < 25$	10	0.89 (0.62–1.29)	0.20	68.9	0.001
$25 \leq BMI < 30$	3	1.62 (1.31–2.00)	<0.001	0.0	0.64
$BMI \geq 30$	3	1.47 (0.96–2.24)	0.55	88.8	<0.001
Missing information	5	1.30 (1.16–1.46)	<0.001	41.6	0.14
Follow-up rate					
$\geq 80\%$	7	1.34 (1.13–1.59)	0.001	61.8	0.015
$< 80\%$	14	1.12 (0.90–1.40)	0.33	78.4	<0.001

$P_1$  for the significance of association of weight fluctuation and the risk of diabetes in each subgroup.  $P_2$  for heterogeneity within each subgroup. BMI, body mass index; CI, confidence interval; RR, relative risk for developing diabetes.

diabetes, the findings are not consistent<sup>10,12,16,30</sup>. The discrepancy in the results might be due to the lack of a standardized definition or measurement of weight cycling, differentiation between intentional and unintentional weight cycling, the participants' age or baseline BMI. Therefore, we carried out subgroup analysis based on these variables. Various reasons could explain the variation in body weight. Several studies showed that individuals with intentional weight cycling had a higher risk of diabetes. However, the association between weight cycling and the risk of developing diabetes was not observed in several subgroup analyses, such as in participants aged  $\leq 60$  years, individuals with normal weight or obesity and in studies using weight cycle as the original measurement for weight cycling. It might be due to the null association in eight reports from the Yokomichi *et al.* study<sup>12</sup> among 21 reports, which might have a potential influence on the association in subgroup analyses. After omission of the Yokomichi *et al.* study, the results of most subgroups were consistent with the original findings. The Yokomichi *et al.* study involved middle-aged employees of private companies who underwent medical checkups. Furthermore, in the study, the point estimate regarding the weight cycling was gain/loss  $>4\%$  of their baseline weight, which was lower than that in other studies<sup>13,30</sup>. This magnitude of weight cycling might not have shown any adverse effect. In addition, the prevalence of diabetes in Japan was at a relative low level compared with that in other countries<sup>37</sup>. The disparity between this result and other Western studies might also be related to ethnicity, which is associated with genetic constitution, living conditions, lifestyle factors and anthropometry<sup>38,39</sup>. However, the null association was also detected in obese individuals (BMI  $\geq 30$  kg/m<sup>2</sup>) even after removing the Yokomichi *et al.* study, suggesting that obesity might have an effect on the risk of diabetes similar to that of weight cycling.

Potential mechanisms for these findings are unclear; intriguing evidence suggests that weight cycling was associated with metabolic disturbance, such as insulin resistance<sup>40</sup>, elevations in triglycerides<sup>41</sup> and abdominal fat accumulation<sup>42</sup>, all of which might contribute to metabolic disease. Another possibility is that weight cycling might be a marker of potential illnesses that have worse prognoses in these participants<sup>9</sup>. In this case, weight cycling could be the early sign and consequence, and not the cause, of the health endpoints, including diabetes and related diseases. It was reported that the risk of developing depression is increased in people with diabetes<sup>43</sup>. Previous research also suggested that participants with a psychological disorder, such as bipolar disorder<sup>44</sup> and depression<sup>45</sup>, are more likely to present with weight cycling. In this case, the cycling in weight could be a consequence rather than the cause of the diabetes. A previous meta-analysis also showed that weight cycling was associated with higher CVD mortality and morbidity<sup>46</sup>, which is the most common cause of morbidity and mortality among individuals with type 2 diabetes<sup>47</sup>.

The present analysis also had several limitations. First, the findings of this meta-analysis are based on observational data;

therefore, the present study could not identify the causal mechanisms driving the observed association between weight cycling and the risk of developing diabetes, which limits the generalizability of the findings. Second, the different definitions and measurements of weight cycling in the included studies might have an important confounding effect, although we carried out detailed subgroup, sensitivity and meta-regression analyses to confirm the robustness of our results. Furthermore, other anthropometric measurements (e.g., waist circumference and waist-to-hip ratio), which were closely related to diabetes, were beyond the scope of our present analyses. Finally, significant heterogeneity was detected among studies, although we carried out detailed subgroup and meta-regression analyses to detect potential sources of heterogeneity.

In summary, the pooled estimates from available cohort studies showed that individuals with weight cycling had a higher risk of developing diabetes. Future physiological studies are required to show the causal links and underlying mechanisms between weight cycling and diabetes.

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## DISCLOSURE

The authors declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Appendix S1** | Search terms.

**Appendix S2** | Additional methods.

**Table S1** | Descriptive characteristics of 14 included articles.

**Table S2** | Quality assessment of individual studies using the Newcastle–Ottawa Scale.

**Table S3** | Meta-regression of factors affecting heterogeneity.

**Table S4** | Sensitivity analysis based on study level for association of weight cycling and risk of diabetes.

**Table S5** | Subgroup analyses for the association between weight cycling and the risk of diabetes after omission of the Yokomichi *et al.* study.

**Figure S1** | Sensitivity analysis based on report level for association of weight cycling and risk of diabetes.

**Figure S2** | Funnel plot for assessment of publication bias.