The impact of weight change on diabetes incidence remains unclear. To clarify the role of weight change as a risk factor for diabetes, the authors assessed the association between weight change and diabetes incidence conditional upon either initial or attained body mass index (BMI). They used 7,837 observations available from repeated measurements of 4,259 participants (men and women aged 20–59 years) in the Dutch population-based Doetinchem Cohort Study (1987–2007) to analyze the association between 5-year weight change and diabetes incidence ($n = 124$) in the subsequent 5 years. When adjusted for initial BMI, 5-year weight change was a significant risk factor for diabetes (odds ratio $= 1.08$, 95% confidence interval: 1.04, 1.13 per kilogram of weight change). However, no significant association was found between weight change and diabetes if the association was adjusted for attained BMI (odds ratio $= 0.99$, 95% confidence interval: 0.94, 1.04 per kilogram of weight change). Results suggest that weight change is associated with diabetes incidence because, conditional upon initial BMI, weight change determines attained BMI. This finding implies that lifestyle interventions can contribute to diabetes prevention because they affect attained BMI. Weight change appears to have no effect on diabetes incidence beyond its effect on attained BMI.

**Abbreviations:** BMI, body mass index; CI, confidence interval; SD, standard deviation.

Obesity is acknowledged as an important risk factor for diabetes (1–8). The pooled “average” relative risk for diabetes is approximately 1.18 per unit increase in body mass index (BMI) (4), but several studies have shown that the impact of BMI on diabetes incidence is larger for BMI measured more proximal to diabetes outcome compared with earlier, remote measures (9–13). Therefore, it is important that weight attained at the end of the weight change period be taken into account if the impact of weight change on diabetes incidence is assessed.

We identified 15 prospective observational studies that explored the association between weight change and incident diabetes ((9–23); Web Table 1, a supplementary table posted on the Journal’s Web site (http://aje.oupjournals.org/)). It seems that only 2 studies took into account attained BMI (11, 18), whereas 2 studies adjusted for “overall weight status” (19) or “average weight” (22) during the weight change period. Most studies (12 of 15) assessed the association with adjustment for initial BMI. Therefore, although many studies have found positive associations between weight change and diabetes, the impact of weight change on diabetes incidence, beyond its effect on attained weight, remains unclear.

In an attempt to clarify this unresolved issue, we start by discussing the implications of using different analytic approaches. Subsequently, we use Dutch data to analyze the association between weight change and diabetes, with adjustment for either initial or attained BMI, and discuss the implications of the different results.

The methodological question of how to disentangle the impact of risk factor level versus risk factor change on
disease incidence was addressed by Hofman in 1983 (24). He pointed out that there are 2 different ways of looking at the impact of risk factor change on disease risk, that each way implies a specific data-analytic approach, and that the obtained results have different implications. With respect to the impact of weight change on diabetes, the association can be explored from what we will call a “prospective” or “retrospective” point of view.

With the prospective approach, we can explore whether, at a certain level of BMI, future weight change is important. For data analysis, this means that the effect of weight change is assessed conditional upon initial BMI (Figure 1A). From Figure 1A it is easy to imagine that, conditional upon initial BMI, weight change determines attained BMI. Persons who lose weight will have lower attained levels of BMI, and persons who gain weight will attain higher levels of BMI. Because both weight loss and low attained BMI are expected to be associated with a lower risk of diabetes, the coefficient for weight change in this analysis could reflect a positive association with diabetes “simply” because weight change determines attained BMI. Results from this approach do not reveal whether weight change is a risk factor for diabetes independent of level of attained BMI.

The retrospective approach explores whether, at a certain level of attained BMI, weight change history is important. In this analysis, the effect of weight change is assessed conditional upon attained BMI (Figure 1B). Figure 1B illustrates that, conditional upon attained weight, previous weight change determines initial BMI. Persons who lost weight started at higher initial levels of BMI, and persons who gained weight started at lower levels; thus, the coefficient for weight change in this model reflects the joint, presumably opposite effects of weight change and initial BMI. A negative coefficient for weight change in this model would imply that initial weight is more important than subsequent weight change, whereas a positive coefficient would imply that weight change has a larger impact than initial weight and affects diabetes incidence beyond its effect on attained BMI.

In the analyses in this paper, we explore the association between weight change and incident diabetes conditional upon either initial or attained BMI. We hypothesize that, conditional upon initial BMI, weight change affects diabetes incidence by affecting attained BMI but that weight change in itself has some additional effect.

MATERIALS AND METHODS

Study population

The Doetinchem Cohort Study is a prospective, observational, population-based Dutch study with 4 measurement rounds (at 5-year intervals) completed between 1987 and 2007. The first measurements took place between 1987 and 1991. In that period, 12,405 inhabitants of Doetinchem, the Netherlands, aged 20–59 years were examined as part of the Monitoring Project on Cardiovascular Disease Risk Factors. Of the participants in the first round (round 1), a random sample of 7,769 were invited to participate in a second examination (round 2: 1993–1997) and again 5 and 10 years later for a third (round 3: 1998–2002) and fourth (round 4: 2003–2007) examination. Included were questionnaires and a physical examination. Details on sampling and data collection procedures are described elsewhere (25).

The study was approved according to the guidelines of the Helsinki Declaration by the external Medical Ethics Committee of the Netherlands Organization of Applied Scientific

Figure 1. Illustration of data analysis to assess the impact of weight change on diabetes incidence, Doetinchem Cohort Study, the Netherlands, 1987–2007. A) Prospective approach: the association is assessed with adjustment for initial body mass index (BMI); this panel illustrates that, conditional upon initial BMI, weight change determines attained BMI. B) Retrospective approach: the association is assessed with adjustment for attained BMI; this panel illustrates that, conditional upon attained BMI, previous weight change determines initial BMI.
Research Institute. All participants gave written informed consent.

**Assessment of weight and weight change**

Body weight and height were measured during each examination. Weight change was calculated between round 1 and round 2 and between round 2 and round 3. Although the actual time between measurements between round 1 and round 2 was approximately 6 years, “5-year weight change” is used throughout this paper. To calculate 5-year weight change, weight change (absolute change in kilograms, weight change relative to initial weight, or absolute change in BMI (weight (kg)/height (m)²)) was divided by the actual time between measurements (in years) and multiplied by 5. Five-year weight change was modeled as a continuous risk factor (with weight loss having a negative value) and also considered in categories: weight loss (>2.0 kg), stable weight (±2.0 kg = reference), small weight gain (2.0–4.0 kg), moderate weight gain (4.0–6.0 kg), and substantial weight gain (>6.0 kg). These categories were based on a stable, sufficiently large reference group and a fair, relatively equal number of cases and observations in each of the remaining categories.

**Other variables**

Demographic and lifestyle characteristics were obtained from self-administered questionnaires completed at home and checked during the examination visits. Biomedical outcomes were obtained from the physical examinations. Characteristics considered as potential confounders were age, gender, menopausal status (men, women with a regular menstrual cycle, or women without a regular cycle), nationality (Dutch or other), prevalent cardiovascular disease (self-reported history of acute myocardial infarction or stroke), and education. Educational level was assessed as the highest level of completed education and was classified into 4 categories: primary school or less, lower vocational or intermediate secondary education, intermediate vocational or higher secondary education, and higher vocational education or university. Lifestyle characteristics considered were leisure-time physical activity (active or inactive), smoking (current, former, or never), alcohol consumption (4 categories), and coffee consumption (cups per day). Potential “biomedical confounders” were systolic blood pressure, diastolic blood pressure, hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive medication use), high density lipoprotein cholesterol, total cholesterol, and cholesterol ratio (total/high density lipoprotein cholesterol). In addition, 5-year changes in blood pressure and cholesterol levels were considered confounders in the retrospective analyses.

**Outcome measurements**

Cases were defined on the basis of self-reported diabetes (Do you have diabetes? yes/no) only. However, most of the self-reported cases of diabetes were verified against information from the general practitioner or pharmacist. Of the 99 (of 124) self-reported cases who could be verified, 88 were confirmed cases with incident type 2 diabetes, 5 were confirmed non-type-2 diabetics, 3 were prevalent type 2 diabetics, and 3 were confirmed nondiabetics. Sensitivity analyses were performed by considering “confirmed incident type 2 diabetes” cases only. In these latter analyses, all self-reported diabetic cases who were not “confirmed incident type 2” were excluded.

**Statistical methods**

We used generalized estimating equation analyses (proc GENMOD in SAS with link = logit, D = binomial, and correlation structure = exchangeable; SAS Institute, Inc., Cary, North Carolina) to assess the association between 5-year weight change and incident diabetes in the subsequent 5 years (Figure 2). Observations used in cluster 1 were initial BMI at round 1, weight change between round 1 and round 2, attained BMI at round 2, and incident diabetes between round 2 and round 3. Observations used in cluster 2 were initial BMI at round 2, weight change between round 2 and round 3, attained BMI at round 3, and incident diabetes between round 3 and round 4. There was a significant negative correlation between repeated weight change observations in cluster 1 and cluster 2 (r = −0.12), and we used the “repeated” statement to control for this correlation.

We applied a prospective approach, with baseline data from round 1 and round 2, to assess the association between weight change and diabetes conditional upon initial BMI (Figure 2A). A retrospective approach with baseline data from round 2 and round 3 was used to assess the association between weight change and diabetes conditional upon attained BMI (Figure 2B).

Persons with prevalent diabetes at round 1 or round 2 were completely excluded; observations from persons with incident diabetes at round 3 were excluded in cluster 2. We excluded observations from women pregnant at round 1 or round 2 from cluster 1 and observations from women pregnant at round 2 or round 3 from cluster 2. Observations from persons with cancer at round 1, round 2, or round 3 or at round 2, round 3, or round 4 were excluded from cluster 1 and cluster 2, respectively.

To adjust for confounders, we explored which individual confounders caused a more than 5% change in the odds ratio for diabetes for any of the 4 weight change categories if they were included in the age- and gender-adjusted models. Subsequently, these confounders were included simultaneously in fully adjusted models but removed if omitting them caused a less than 5% change. Initially, “cluster” was included in each model but was finally removed since it did not confound or modify the associations.

**RESULTS**

There were 7,837 observations available for the analyses. A total of 4,259 participants had observations in cluster 1, and 3,578 of these participants had repeated observations in cluster 2 (Figure 2). Mean initial BMI was 24.8 kg/m² (standard deviation (SD), 3.4). Mean 5-year weight change was a gain of 2.2 kg (SD, 4.0), consistent with a 3.1% (SD, 5.6) increase.
from initial weight. Among persons who gained weight (74% of the observations), mean 5-year weight gain was 3.9 kg (SD, 3.1). Among persons in the substantial weight gain category, median weight gain was 8.0 kg (range, 6–29). Persons who lost weight (26% of the observations) lost 2.4 kg (SD, 2.4) on average. Among persons in the weight loss category, median weight loss was 3.5 kg (range, 2–24). The negative correlation between initial BMI and weight change was weak ($r = 0.06$), but significant. The positive correlation between weight change and attained BMI ($r = 0.35$) was much stronger. Mean attained BMI was 25.6 kg/m$^2$ (SD, 3.6).

During follow-up, 124 persons developed diabetes. The risk of developing diabetes within 5 years was 1.6% (Table 1). After adjustment for age and gender, initial BMI, 5-year weight change, and attained BMI were all crudely associated with diabetes incidence. The adjusted odds ratios were 1.24 (95% confidence interval (CI): 1.20, 1.29) per kg/m$^2$ for initial BMI and 1.23 (95% CI: 1.19, 1.27) per kg/m$^2$ for attained BMI. The adjusted odds ratio for 5-year weight change as a continuous variable was 1.08 (95% CI: 1.03, 1.14) per kilogram change.

**Prospective approach**

The crude association between weight change and diabetes remained essentially unchanged after adjustment for initial BMI and baseline characteristics (Table 2). The fully adjusted odds ratios for 5-year weight change were 1.08 (95% CI: 1.04, 1.13) per kilogram change, 1.08 (95% CI: 1.04, 1.12) per percentage change from initial weight, and 1.27 (95% CI: 1.12, 1.44) per unit change in BMI. Persons who gained a substantial amount of weight had more than a doubled risk of diabetes compared with persons whose weight was stable: adjusted odds ratio = 2.4 (95% CI: 1.4, 4.0).

We found that the odds ratio for diabetes associated with 5-year weight change (odds ratio = 1.27, 95% CI: 1.12, 1.44 per unit of BMI) was not larger than the odds ratio for diabetes associated with a 1-unit difference in attained BMI (odds ratio = 1.23, 95% CI: 1.19, 1.27). This finding suggests that the association between weight change and diabetes might be explained by differences in attained level of BMI (also refer to Figure 1A).

The impact of weight change (and attained BMI) on diabetes incidence was slightly modified by initial BMI ($P = 0.12$ for interaction). The adjusted odds ratios for diabetes for persons with an initial BMI of <30 were 1.38 (95% CI: 1.15, 1.65) per 1-unit change in BMI and 1.32 (95% CI: 1.22, 1.42) for a 1-unit difference in attained BMI. For initially obese persons, the corresponding odds ratios were 1.14 (95% CI: 0.98, 1.34) and 1.11 (95% CI: 1.02, 1.20).

**Retrospective approach**

The crude association between 5-year weight change and diabetes disappeared completely after adjustment for attained BMI (Table 3). The fully adjusted odds ratios for 5-year weight change were 0.99 (95% CI: 0.94, 1.04) per kilogram of weight change, 0.99 (95% CI: 0.95, 1.03) per percentage change from initial weight, and 0.97 (95% CI: 0.84, 1.12) per unit change in BMI. This association was not

![Figure 2. Illustration of data analysis to assess the association between weight change and diabetes incidence, Doetinchem Cohort Study, the Netherlands, 1987–2007. A) Prospective approach: the association is assessed conditional upon initial body mass index (BMI) and initial baseline characteristics; this panel illustrates how observations from 4 repeated measurements are combined and gives the number of participants (observations) and cases in each cluster. B) Retrospective approach: the association is assessed conditional upon attained BMI and attained baseline characteristics; this panel illustrates how the data from 4 repeated measurements are combined and gives the number of participants (observations) and cases in each cluster. R, round.](image)
modified by level of attained BMI: the association was similar for persons with an attained BMI of less than 30 and persons with an attained BMI of more than 30.

**Sensitivity analyses**

The results remained essentially similar when the analyses were based on cases with confirmed incident type 2 diabetes only. Fully adjusted odds ratios were 1.12 (95% CI: 1.07, 1.17) per kilogram of weight change with the prospective approach and 1.02 (95% CI: 0.96, 1.08) per kilogram of change with the retrospective approach.

**DISCUSSION**

Our study showed that short-term weight change was associated with diabetes incidence in crude analyses as well as after adjustment for initial BMI. However, weight change was not associated with diabetes incidence if attained BMI was considered. Taken together, our results seem to imply that weight change does not affect diabetes incidence beyond its effect on attained BMI.

A literature search yielded 15 previous observational studies in which the association between weight change and diabetes was explicitly addressed ([9–23], Web Table 1). There were large differences between these studies with respect to duration of the weight change period (ranging from 2 to more than 20 years) as well as duration of follow-up (ranging from 0 to more than 20 years). Eleven studies compared diabetes risk for different categories of weight change with that for a “stable” reference group. Nine studies also assessed a continuous association between weight change and diabetes. Weight change was generally assessed as absolute change in kilograms or units of BMI.

Most studies assessed the association between weight change and diabetes with adjustment for initial BMI, and most of these studies reported positive associations. For example, Colditz et al. (12) showed that weight gain from young adulthood until early midlife increased diabetes risk for women in the Nurses’ Health Study and stressed the importance of maintaining a constant weight throughout adult life. Oguma et al. (9) reported very similar findings for men and concluded that avoidance of weight gain is important even for those who are initially lean. Mishra et al. (16) did not find a continuous effect of short-term

**Table 1.** Absolute and Relative Risks (Odds Ratios) of 5-Year Diabetes Incidence According to Participants’ Baseline Characteristics and Weight Variables, Doetinchem Cohort Study, the Netherlands, 1987–2007

<table>
<thead>
<tr>
<th>No. of Observations</th>
<th>No. of Cases</th>
<th>Cumulative Diabetes Incidence, %</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>7,837</td>
<td>124</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>3,831</td>
<td>71</td>
<td>1.9</td>
<td>1.0</td>
</tr>
<tr>
<td>4,006</td>
<td>53</td>
<td>1.3</td>
<td>0.7</td>
<td>0.5, 1.1</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–49</td>
<td>4,634</td>
<td>34</td>
<td>0.7</td>
<td>1.0</td>
</tr>
<tr>
<td>50–70</td>
<td>3,203</td>
<td>90</td>
<td>2.8</td>
<td>3.9, 2.6, 5.8</td>
</tr>
<tr>
<td><strong>Initial BMI, kg/m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>4,476</td>
<td>17</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>25–30</td>
<td>2,837</td>
<td>66</td>
<td>2.3</td>
<td>4.4, 2.5, 7.6</td>
</tr>
<tr>
<td>&gt;30</td>
<td>520</td>
<td>41</td>
<td>7.9</td>
<td>15.7, 8.7, 28.3</td>
</tr>
<tr>
<td><strong>5-year weight change</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gained &gt;6.0 kg</td>
<td>1,139</td>
<td>29</td>
<td>2.6</td>
<td>2.8, 1.7, 4.5</td>
</tr>
<tr>
<td>Gained 4.0–6.0 kg</td>
<td>1,141</td>
<td>20</td>
<td>1.8</td>
<td>1.6, 0.9, 2.7</td>
</tr>
<tr>
<td>Gained 2.0–4.0 kg</td>
<td>1,663</td>
<td>19</td>
<td>1.1</td>
<td>0.9, 0.5, 1.6</td>
</tr>
<tr>
<td>Stable weight, ±2.0 kg</td>
<td>2,986</td>
<td>42</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Lost &gt;2.0 kg</td>
<td>895</td>
<td>14</td>
<td>1.6</td>
<td>1.0, 0.6, 1.9</td>
</tr>
<tr>
<td><strong>Attained BMI, kg/m²</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>3,665</td>
<td>11</td>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>25–30</td>
<td>3,324</td>
<td>57</td>
<td>1.7</td>
<td>4.2, 2.2, 8.1</td>
</tr>
<tr>
<td>&gt;30</td>
<td>838</td>
<td>56</td>
<td>6.7</td>
<td>17.3, 8.9, 33.5</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

* 3,578 of 4,259 participants contributed observations to both clusters (Figure 2).
* Incident cases (self-reported diabetes) in cluster 1 or cluster 2 (Figure 2).
* Adjusted for age, age × age, and gender.
* Attained age (after the 5-year weight change period, Figure 2).
weight change on diabetes incidence after adjustment for initial BMI, but women with a high weight gain had a higher risk of diabetes compared with women of stable weight.

Only 4 studies examined the association between weight change and diabetes while taking into account attained (11, 18) or “average” (19, 22) weight. In one other study (23), attained BMI was used as a stratification variable to assess the impact of duration of overweight and obesity on diabetes risk. Brancati et al. (11) reported that weight change between ages 25 and 45 years was crudely associated with diabetes incidence after age 50 years but not after adjustment for attained BMI. The significant, continuous association between weight change and diabetes also appears beneficial in preventing diabetes, but at least substantial weight gain should be avoided.

However, Black et al. (18) found that the risk of diabetes at age 51 years increased by weight gain from age 20 to 31 years but not by weight gain from age 33 to 44 years or by recent weight gain from age 44 to 51 years, suggesting that the impact of weight change might differ between specific stages of life. In the study by Waring et al. (19), crude analyses showed that weight change between age 40 and 50 years was not associated with diabetes incidence after age 50 years, maybe because of the long duration of follow-up in this study (average, 24 years); this negative result remained after adjustment for either “overall weight status” during the weight change period or “recent” weight gain. In the study by Field et al. (22), the impact of weight gain between 1989 and 1993 appeared to have a larger impact on diabetes incidence in the subsequent 6 years than “recent” weight gain in the 4-year period prior to the development of diabetes, after adjustment for average weight during this latter period. Again, the findings suggest that the impact of weight change might be different during different periods of life.

We explored the impact of weight change on diabetes incidence from 2 different points of view. The results from the prospective analyses showed that substantial weight gain is associated with a higher risk of diabetes; persons who gain more than 6 kg over 5 years have more than a doubled risk of developing diabetes in the subsequent 5 years compared with persons of stable weight. The significant, continuous association between weight change and diabetes also suggests that weight loss is associated with a lower risk of diabetes and underscores the potential benefits of weight loss interventions. Weight loss over 5 years was also associated with a lower risk of developing diabetes for men in the British regional heart study (17), but there was no evidence that weight loss was associated with a lower risk of major cardiovascular disease events. On the other hand, men who gained weight (>10% in 5 years) had a higher risk of diabetes as well as of cardiovascular disease. On the basis of these results, it seems justified to conclude that weight loss appears beneficial in preventing diabetes, but at least substantial weight gain should be avoided.

The results from our retrospective analyses suggest that recent weight change history is not an independent risk factor for diabetes. This finding could be of interest for clinicians who have to decide upon possible treatments, for epidemiologists engaged in risk prediction, or for those interested in the causation of diabetes. We showed...
(Figure 1B) that the results from a retrospective analysis are difficult to interpret and that potential effects of initial BMI and weight change cannot be separated. However, together with our results from the prospective approach, we showed that the impact of weight change on diabetes incidence can be explained through its effect on attained BMI. Our results imply that weight change history is not an independent risk factor for diabetes and not an important additional factor to consider in clinical or epidemiologic prediction models (26–28). However, since only a few former studies have applied this “retrospective approach,” further research is required to explore the impact of short-term weight change, long-term weight change, and weight change at different stages of life.

The Doetinchem Cohort Study is a population-based study with repeated measurements for more than 4,000 Dutch men and women of different ages. The comprehensiveness of the study enabled us to adjust for many lifestyle variables such as physical activity, alcohol consumption, and smoking, as well as for biomedical factors such as blood pressure and cholesterol. Because of the physical examinations in each round, all our analyses were based on measured weight variables, in contrast to many other studies that have to rely on self-reported weight (Web Table 1).

There were also some limitations. First, identification of cases was based on self-reported diabetes, and we might have missed persons with undiagnosed diabetes. This potential misclassification could have caused underestimation of the associations found. Self-reported diabetes in our study appeared to be quite accurate, and our results remained essentially similar when the analyses were restricted to diabetic cases with confirmed incident type 2 diabetes. Second, we did not know the reasons for weight loss. Intentional weight loss could be advised by a physician for persons with unfavorable risk profiles, and unintentional weight loss might be caused by preclinical disease. Although both reasons could cause weight loss to be associated with a higher risk of diabetes (14, 17), our results suggest that weight loss is associated with a lower risk of diabetes. Finally, information about weight cycling during the 5-year periods was not available. However, although weight cycling appeared to be associated with diabetes incidence in both the Framingham Heart Study (19) and the Nurses’ Health Study II (22), the associations between weight cycling and diabetes disappeared in both studies after adjustment for, respectively, “overall weight status” (19) or attained BMI (22).

In conclusion, weight change is associated with diabetes incidence because, conditional on initial BMI, weight change determines attained BMI. This finding implies that lifestyle interventions can contribute to diabetes prevention because they can influence attained BMI. Weight change history appears to have no effect on diabetes incidence beyond its effect on attained BMI.

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