Brief Original Contribution

Five-Year Changes in Biologic Risk Factors and Risk of Type 2 Diabetes: Are Attained But Not Initial Risk Factor Levels of Importance?

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Initially submitted June 8, 2011; accepted for publication March 23, 2012.

Independent effects of changes in biologic risk factors on type 2 diabetes incidence remain unclear. The authors examined whether associations between changes in biologic risk factors and diabetes risk are driven by initial or attained risk factor levels. Biologic risk factors were measured at baseline and at each 5-year interval follow-up (rounds 2, 3, and 4) among 4,204 initially healthy men and women, aged 20–59 years, participating in the Dutch Doetinchem Cohort Study (1987–2007). Time-dependent Cox regression analyses were used to analyze associations between changes in waist circumference, blood pressure, and high density lipoprotein cholesterol (HDL cholesterol) and incident diabetes, adjusted for initial or attained levels; 130 diabetes cases occurred during 9 years of follow-up. Five-year increases in waist circumference and blood pressure and decreases in HDL cholesterol were positively associated with risk of diabetes after adjustment for initial levels but no longer after adjustment for attained levels: waist circumference (hazard ratio (HR) = 0.86, 95% confidence interval (CI): 0.69, 1.07), systolic blood pressure (HR = 0.96, 95% CI: 0.84, 1.10), diastolic blood pressure (HR = 0.96, 95% CI: 0.87, 1.06), and HDL cholesterol (HR = 0.91, 95% CI: 0.81, 1.01). In conclusion, the associations between changes in biologic risk factors and risk of diabetes are mainly driven by the attained levels. Hence, not the prior changes, but the attained levels seem to be of importance with regard to diabetes risk.

blood pressure; cholesterol, HDL; risk factors; type 2 diabetes; waist circumference

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; HDL cholesterol, high density lipoprotein cholesterol; HR, hazard ratio; SBP, systolic blood pressure.

Clinicians often monitor changes in biologic risk factors over a period of years but, in contrast to the large number of studies documenting independent associations between baseline obesity (1–5), high blood pressure (6–8), and low high density lipoprotein cholesterol (HDL cholesterol) (4, 5, 9) and risk of type 2 diabetes, little is known about how sequential changes may be related to future risk. A few studies have reported that changes in weight (10, 11), waist circumference (10, 12, 13), blood pressure (6, 14), and HDL cholesterol (14) are positively associated with diabetes. However, these studies assessed associations with adjustment for initial risk factor levels only. It was suggested earlier that this approach does not examine the true independent effects of changes on disease risk (15) and that the observations may reflect the effects of attained levels. Indeed, we recently showed that weight change was no longer associated with diabetes when we adjusted for attained body mass index (16). This implies that weight change has no effect on diabetes risk beyond its effect on attained levels. The purpose of the present study was to extend these findings to other biologic risk factors in the same population-based study. We examined whether associations between changes in waist circumference, blood pressure, and HDL cholesterol and incidence of type 2 diabetes are driven by the initial or attained risk factor levels.
MATERIALS AND METHODS

Population and measurements

Details of the Doetinchem Cohort Study have been described elsewhere (17). In brief, the Doetinchem Cohort Study is a prospective study with 4 measurement rounds (at 5-year intervals) that included a general population sample of 7,769 men and women aged 20–59 years during the first examination round designated “R1” (1987–1991). Second (R2: 1993–1997), third (R3: 1998–2002), and fourth (R4: 2003–2007) examination rounds have been completed. In each round, height and weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and nonfasting HDL cholesterol were measured. Furthermore, waist circumference and random glucose were measured from R2 onward. In each round, a questionnaire was administered on demographics (e.g., age, education), lifestyle factors (e.g., smoking, physical activity), presence of chronic diseases, and medication use. Incident diabetes was defined on the basis of self-report or a nonfasting blood glucose concentration of 11.1 mmol/L or more. Information on vital status was obtained through linkage with the municipal administration registries. For the present study, a total of 4,661 people who participated for a minimum of 3 examination rounds were eligible. Persons with prevalent diabetes at R1 (n = 28), type 1 diabetes (n = 5), or cancer (n = 325) or with missing data about development of diabetes (n = 10) or the determinants waist circumference, blood pressure, and HDL cholesterol (n = 43) were excluded.

Statistical analyses

In contrast to our previous paper (16), time-dependent Cox regression models were used to study whether associations between changes in biologic risk factors and diabetes risk are driven by initial or attained risk factor levels (Figure 1). For this purpose, changes between R1 and R2, initial levels at R1, and attained levels at R2 were used to estimate the risk for incident diabetes between R2 and R3. Changes between R2 and R3, initial levels at R2, and attained levels at R3 were used to estimate the risk for incident diabetes between R3 and R4. As waist circumference was measured from R2 onward, changes between R2 and R3 could be related to incident diabetes only between R3 and R4. Changes were calculated between R1 and R2 and between R2 and R3 and were included as time-dependent variables in the Cox regression analyses. The resulting hazard ratios can be interpreted as the risk of 5-year changes in risk factors for the development of diabetes in the following 5 years. Diabetes risk was determined per increment of 5 cm in waist circumference, 10 mm Hg in SBP, and 5 mm Hg in DBP and per decrements of 0.1 mmol/L in HDL cholesterol.

In the analyses of changes between R1 and R2, the period at risk for diabetes began at R2. Likewise, in the analyses of changes between R2 and R3, the period at risk for diabetes began at R3. Participants with a diagnosis of diabetes during follow-up were censored at the date of diagnosis or at the date of the physical examination during which a high blood glucose concentration was measured. All others were followed until the date of death or the date of the last physical examination they attended. Persons with incident type 2 diabetes between R1 and R2 (n = 46) were excluded for the analyses of diabetes incidence between R2 and R3. Likewise, in Cox regression, those who developed diabetes between R2 and R3 (n = 62) were censored from the data set for the analyses of diabetes incidence between R3 and R4.

We first present the hazard ratios for the change in each of the biologic risk factors adjusted for age and sex (model 1). Model 2 includes additional adjustment for the initial or attained values. Multivariable model 3 additionally included highest educational level (3 categories) and time-dependent body mass index (continuous), smoking status (3 categories), alcohol intake (4 categories), physical activity (dichotomous), parental history of diabetes (dichotomous), and antihypertensive and cholesterol-lowering medications (dichotomous).

The presence of effect modification between initial values of biologic risk factors and mean changes from R1 to R2 and from R2 to R3 was tested by incorporating their product terms in the models. All analyses were performed by using SAS, version 9.1, statistical software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 presents the baseline characteristics of the study population. During the follow-up (mean follow-up, 9.2 years), 130 cases of incident diabetes occurred (62 between R2 and R3 and 68 between R3 and R4). Persons with incident diabetes had a statistically significant greater increase in SBP and a lower increase in HDL cholesterol compared
After adjustment for age and sex, 5-year increases in waist circumference and blood pressure and decreases in HDL cholesterol were all generally positively associated with diabetes risk and statistically significantly so for SBP (Table 2, model 1). After adjustment for initial levels and confounders, 5-year increases in waist circumference (hazard ratio (HR) = 1.32, 95% confidence interval (CI): 1.07, 1.64 per 5 cm) and blood pressure (SBP: HR = 1.26, 95% CI: 1.12, 1.41 per 10 mm Hg; DBP: HR = 1.19, 95% CI: 1.08, 1.30 per 5 mm Hg) and decreases in HDL cholesterol (HR = 1.13, 95% CI: 1.02, 1.26 per 0.1 mmol/L) were positively associated with risk of diabetes (Table 2, model 3). However, Table 3, model 3, shows that changes in biologic risk factors were no longer associated with diabetes after adjustment for attained biologic risk factor levels and confounders—waist circumference (HR = 0.86, 95% CI: 0.69, 1.07), SBP (HR = 0.96, 95% CI: 0.84, 1.10), DBP (HR = 0.96, 95% CI: 0.87, 1.06), and HDL cholesterol (HR = 0.91, 95% CI: 0.81, 1.01). Similar results were obtained with the analysis of longer term (R1–R3) changes (data not shown). There was no evidence of effect modification between initial levels and change in risk factors, as no statistically significant interaction terms were observed (data not shown).

**DISCUSSION**

We previously reported that weight change has no effect on diabetes risk beyond its effect on attained body mass index (16). In the present study, we extended these findings to other risk factors. We showed that 5-year increases (waist circumference and blood pressure) and decreases (HDL cholesterol) in biologic risk factors were positively associated with risk of diabetes after adjustment for initial levels, but no longer after adjustment for attained levels. Considered together, these findings imply that the associations between changes in biologic risk factors and risk of diabetes seem to be mainly driven by the attained levels. Thus, given an
individual’s attained level of waist circumference, blood pressure, or HDL cholesterol, the changes over the previous 5 years do not seem to affect the subsequent risk of diabetes.

The main advantages of this study are its prospective nature, large sample size, and the availability of repeated measurements of risk factors. A limitation is the relatively small number of diabetes cases, which may have affected the statistical power to detect associations after adjustment for highest level of completed education (low, medium, high) and time-dependent body mass index (continuous), smoking status (never, past, current), alcohol intake (none, light, moderate, heavy), physically active (yes, no), parental history of diabetes (yes, no), antihypertensive medication (yes, no), and cholesterol-lowering medication (yes, no).

In conclusion, in this population-based longitudinal study, 5-year changes in biologic risk factors were associated with diabetes incidence after adjustment for initial levels, but no longer after adjustment for attained levels. The associations between changes in biologic risk factors and risk of diabetes are therefore likely to be driven mainly by the attained levels. Hence, not the prior changes, but the attained levels seem to be of importance with regard to the risk of diabetes.

ACKNOWLEDGMENTS

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REFERENCES


### Appendix Table 1. Mean 5-Year Changes (SD) in Biologic Risk Factors in the Total Study Population and According to Diabetes Incidence, Doetinchem Cohort Study, the Netherlands, 1987–2007

<table>
<thead>
<tr>
<th>Biologic Risk Factor</th>
<th>Total Population</th>
<th>Persons Without Incident Diabetes</th>
<th>Persons With Incident Diabetes</th>
<th>P Value&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.83 (1.01)</td>
<td>0.83 (1.00)</td>
<td>0.90 (1.31)</td>
<td>0.44</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>2.88 (6.26)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.86 (6.28)</td>
<td>2.91 (5.44)</td>
<td>0.92</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>3.84 (7.89)</td>
<td>3.73 (7.81)</td>
<td>7.30 (9.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>2.23 (5.42)</td>
<td>2.24 (5.38)</td>
<td>1.83 (6.72)</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.05 (0.13)</td>
<td>0.06 (0.13)</td>
<td>0.01 (0.12)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviations: HDL cholesterol, high density lipoprotein cholesterol; SD, standard deviation.


<sup>b</sup> Mean changes are calculated as follows: ((biologic risk factors at R2 – biologic risk factors at R1) + (biologic risk factors at R3 – biologic risk factors at R2))/2. As waist circumference was measured from R2 onward, the mean change between R2 and R3 was calculated only.

<sup>c</sup> For mean changes in risk factors, people without incident diabetes versus people with incident diabetes using the *t*-test.

<sup>d</sup> Body mass index: weight (kg)/height (m)<sup>2</sup>.

<sup>e</sup> The mean change between R2 and R3 is based on 4,142 persons as waist circumference is related to incident diabetes between R3 and R4 only.

### Appendix Table 2. Correlations and *P* Values Between Biologic Risk Factor Changes and Initial and Attained Values, Doetinchem Cohort Study, the Netherlands, 1987–2007<sup>a</sup>

<table>
<thead>
<tr>
<th>Biologic Risk Factor Change</th>
<th>R1 Initial Values</th>
<th>R2 Initial Values</th>
<th>R2 Attained Values</th>
<th>R3 Attained Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson’s <em>r</em></td>
<td><em>P</em> Value</td>
<td>Pearson’s <em>r</em></td>
<td><em>P</em> Value</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1–R2</td>
<td>−0.34</td>
<td>&lt;0.0001</td>
<td>0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R2–R3</td>
<td>−0.32</td>
<td>&lt;0.0001</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1–R2</td>
<td>−0.44</td>
<td>&lt;0.0001</td>
<td>0.52</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R2–R3</td>
<td>−0.47</td>
<td>&lt;0.0001</td>
<td>0.50</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1–R2</td>
<td>−0.06</td>
<td>0.0003</td>
<td>0.58</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>R2–R3</td>
<td>−0.27</td>
<td>&lt;0.0001</td>
<td>0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1–R2</td>
<td>−0.21</td>
<td>&lt;0.0001</td>
<td>0.35</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Abbreviation: HDL cholesterol, high density lipoprotein cholesterol.