Major Stressful Life Events in Relation to Prevalence of Undetected Type 2 Diabetes

The Hoorn Study

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OBJECTIVE — To test whether chronic psychological stress is positively associated *1*) with the prevalence of type 2 diabetes; *2*) with visceral adiposity; and to test whether *3*) the relationship between stress and diabetes is mainly mediated by visceral adiposity.

RESEARCH DESIGN AND METHODS — In a general Caucasian population aged 50–74 years without a history of diabetes (n = 2,262), the number of major stressful life events experienced during the past 5 years was assessed by self-report before the administration of an oral glucose tolerance test.

RESULTS — Diabetes was newly diagnosed among 5% of the subjects. The number of stressful events was positively associated with the prevalence of hitherto undetected diabetes. The highest quintile had a 1.6-fold (95% CI 1.0–2.6) increased probability of undetected diabetes compared with the remaining four quintiles ($P < 0.05$ by logistical regression analysis adjusted for age and sex). This increased probability remained significant after additional adjustment for family history of diabetes, heavy alcohol consumption, physical activity, and low level of education. The number of stressful events was weakly positively associated with waist-to-hip ratio (WHR) (men, $P < 0.01$; women, $P = 0.05$ by multiple regression analysis adjusted for age). The age- and sex-adjusted association between stress and diabetes was only marginally reduced by adding the WHR into the logistical regression model (odds ratio 1.5 [0.9–2.4]; $P = 0.08$).

CONCLUSIONS — These cross-sectional findings are partially consistent with Björntorp's theory that stressful life events, which indicate chronic psychological stress, are indeed associated with undetected type 2 diabetes and with visceral adiposity. However, in this white middle-aged population, visceral adiposity does not seem to be the main link between stress and diabetes.

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This study deals with the question "Can psychological stress be one of the factors related to the development of type 2 diabetes?" An interesting theory on the biological plausibility of this stress–diabetes association has been formulated by Björntorp (1,2). This theory states that perceived psychological stress with a defeatist or helplessness reaction leads to an activation of the hypothalamo-pituitary-adrenal axis. This in turn results in endocrine abnormalities, including high cortisol and low sex steroid levels, that antagonize the actions of insulin. In addition, this hormonal imbalance causes visceral adiposity, which plays an important role in diabetes and cardiovascular disease by contributing to the development of insulin resistance (1,2). In animal studies, stressful situations have been shown to induce hyperglycemia (3). Moreover, several studies have reported that psychological stress can induce hyperglycemia in individuals with diabetes (3,4). However, no epidemiological support has been presented so far for the hypothesis that psychological stress can contribute to the onset of type 2 diabetes.

How should we measure psychological stress? We chose to ask subjects about major life events experienced during the past 5 years. Our premise is that these kinds of experiences, such as the death of a loved one, cause major psychological stress, including feelings of helplessness, in almost every individual. In our view, this premise holds true, regardless of individual coping ability, although coping ability will determine how strongly feelings of helplessness predominate and will influence the length and the success of the adaptation period.

The present study has a cross-sectional design, so causality cannot be studied. However, by focusing on the association of psychological stress with cases of hitherto undetected diabetes, we ruled out the possibility that the disease itself influenced stress measurement. These numbers of undetected cases are considerable, because the onset of type 2 diabetes is insidious (5,6). A clinical diagnosis is usually made ~4–7 years after the beginning of the disease (7).

To test the Björntorp theory, we investigated the following hypotheses in a general middle-aged population: chronic psychological stress is positively associated *1*) with the prevalence of hitherto undetected type 2 diabetes; *2*) with visceral adiposity; and *3*) the relationship between chronic psychological stress and undetected diabetes is mainly mediated by visceral adiposity.

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Abbreviations: OGTT, oral glucose tolerance test; OR, odds ratio; WHR, waist-to-hip ratio.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Prevalence of undetected diabetes by single stressful life events in a white population aged 50–74 years (*n = *2,262)*

	Subjects responding "yes" (*n*)	% with diabetes*	OR (95% CI)†
Nonwork event			
Serious or long-lasting illness of a child	106	4.4	0.8 (0.3–2.1)
Death of a child	26	3.2	0.6 (0.1–4.5)
Serious or long-lasting problems with a child	224	6.4	1.4 (0.8–2.6)
Serious or long-lasting problems with a partner	180	5.4	1.2 (0.6–2.1)
Death of a partner	130	10.6‡	1.9 (1.0–3.6)
Death of a relative	1,251	5.6	1.4 (0.9–2.1)
Serious or long-lasting financial problems	114	6.0	1.6 (0.6–3.8)
Moving from a house	561	6.9‡	1.6 (1.1–2.4)
Death of a friend	568	4.2	0.7 (0.5–1.2)
End of an intense relationship	225	5.1	1.1 (0.6–2.1)
Work-related event			
Retirement	205	2.4	0.6 (0.2–1.6)
Disability for work >1 year	146	4.2	1.4 (0.6–3.7)
Forced job change	43	5.1	1.7 (0.4–7.8)
Serious or long-lasting work problems	80	4.0	1.5 (0.4–5.1)

*Prevalence data adjusted for age and sex by analysis of covariance; †ORs adjusted for sex and age with 95% CIs concerning the relationship of reporting a single event (yes/no) with prevalence of undetected diabetes; ‡$P < 0.05$.

RESEARCH DESIGN AND METHODS

Study population

From 1989 to 1992, a population-based survey of glucose tolerance was carried out in the Dutch city of Hoorn, a medium-size town of about 57,000 residents with a mixed rural and urban population. The eligible population of the Hoorn Study consisted of 3,553 men and women (aged 50–74 years) randomly selected from the municipal registry. The response rate was 71%, which resulted in 2,540 participants. From 93% of the 1,013 nonparticipants, we obtained relevant information indicating that no substantial participation bias existed. We excluded 56 non-Caucasians (Caucasian ethnicity was defined as having at least three grandparents from European or Mediterranean countries). Of the remaining 2,484 subjects, 104 individuals responded "yes" to the question "Have you ever been diagnosed with diabetes?" The study population thus consisted of 2,380 individuals without a history of diabetes.

Assessment of chronic psychological stress

As an indicator of chronic psychological stress, we counted the number of major stressful life events experienced during the past 5 years. We chose a simplified version of the questionnaire "Serious Life Events," which was used in another Dutch survey (8). All questions concerned events that are known to be major stressors (Table 1). The questions on perception of and social support during each event were excluded, and four items from a Dutch questionnaire on recently experienced events were added: retirement, death of a friend, moving from a house, and ending an intense relationship (9). The final list thus consisted of 10 nonwork events and 4 work-related events (see Table 1). Subjects' stress questionnaires were completed at home before the oral glucose tolerance test (OGTT) and were checked at the research center during a personal interview. Questionnaires with missing data for more than one stressful event were excluded from the analysis.

A frequently used instrument in research on the stress–illness association is the Holmes and Rahe Social Readjustment Scale (10). This instrument has been tested in different populations. However, for the present study, it was less appropriate. We were mainly interested in events that can cause feelings of helplessness, whereas the Holmes and Rahe Social Readjustment Scale focuses on the effect of change as such, including also presumably happy events like marriage, outstanding personal achievement, and vacations. Overlap exists between both scales: 8 of our 10 nonwork stressful events and all 4 work-related events are also mentioned in the Holmes and Rahe Social Readjustment Scale, although the precise wording of the corresponding items is different (10).

Other measurements

Diabetes was studied using an OGTT according to 1985 World Health Organization recommendations (11). Criteria for newly detected diabetes were fasting plasma glucose ≥7.8 mmol/l and/or 2-h postload plasma glucose ≥11.1 mmol/l (11). Glucose was measured with a glucose dehydrogenase method (Merck, Darmstadt, Germany). Immunospecific insulin was measured in serum by a double-antibody radioimmunoassay (lot SP21; Linco Research, St. Louis, MO), in which proinsulin and des (31,32) proinsulin cross-react by <0.2% (12). Visceral adiposity is reflected in an increased waist-to-hip ratio (WHR), which was measured with standard procedures (13).

Family history of diabetes, physical activity, heavy alcohol use, and low level of education were all self-reported. Family history was defined as positive when any of the subject's grandparents, parents, brothers, sisters, or children had a history of diabetes. Physical activity was measured with a questionnaire originally designed for use in elderly Dutch men (14). Because our participants were middle-aged and also included women, we adapted this questionnaire slightly, which resulted in nine yes/no questions. Participants were asked whether they were currently active in sports, bicycling, gardening, walking, doing odd jobs in and around the house, walking up and down the stairs, doing household activities, shopping daily for food, and working (paid or unpaid employment). The questions were equally weighted, so the physical activity score ranged from 0 to 9. Alcohol intake was measured by asking participants how many glasses of beer, wine, or spirits a week they consume on average. One alcohol unit was counted as 10 g of alcohol. Only the subjects' present situation was recorded because self-reported data on physical activity or alcohol consumption in the past tend to be unreliable. We assumed that, in our middle-aged population, the level of both parameters would be rather stable. Low level of education was defined as having completed primary school only.

Table 2—*Subject characteristics by number of nonwork stressful life events in a white population aged 50–74 years* (n = *2,262)*

	Number of nonwork stressful life events during the past 5 years (maximum = 10)					
	0	1	2	3	≥4	*P**
n	482	820	558	241	161	—
Sex (% female)	50	52	55	56	61	<0.01
Age (years)	60 ± 7	61 ± 7	62 ± 7	63 ± 7	62 ± 8	<0.0001
Diabetes in family (%)	24	25	31	26	28	0.07
Heavy alcohol use (% consuming >30 g/day)	6.5	7.9	8.8	6.3	5.7	0.85
Physical activity (*n* of regular activities, maximum = 9)	5.8 ± 1.5	5.5 ± 1.6	5.7 ± 1.6	5.6 ± 1.7	5.7 ± 1.7	0.29
Low level of education (%)	30	34	32	35	35	0.18
BMI (kg/m^2)						
Men	26 ± 3	26 ± 3	26 ± 3	27 ± 3	26 ± 3	<0.05
Women	27 ± 4	27 ± 4	27 ± 4	27 ± 5	27 ± 5	0.41
WHR						
Men	0.94 ± 0.07	0.95 ± 0.06	0.95 ± 0.06	0.96 ± 0.07	0.96 ± 0.07	<0.01
Women	0.84 ± 0.07	0.85 ± 0.07	0.85 ± 0.08	0.85 ± 0.08	0.85 ± 0.07	0.05
Fasting specific insulin (pmol/l)†	76 (57, 106)	77 (57, 108)	75 (58, 106)	82 (60, 111)	79 (55, 111)	0.30

Data are *n*, %, means ± SD, or medians (20th, 80th percentiles). Except for insulin values, all values were adjusted for age and sex by analysis of covariance (BMI and WHR were adjusted only for age). **P* values from logistical regression analysis for dichotomous variables and from multiple regression analysis for continuous variables. In all analyses, age and sex were added as covariates. When age or sex was the dependent variable, we corrected only for age or sex, respectively; †*P* value from analysis with log-transformed insulin values.

Statistical analysis

Age- and sex-adjusted values of variables were calculated with analysis of covariance. The association between the number of stressful events (independent variable) and the prevalence of undetected diabetes (dependent variable) was analyzed with a multiple logistical regression analysis involving age, sex, family history of diabetes, physical activity, heavy alcohol consumption, low level of education, and WHR as covariates. Two-tailed *P* values <0.05 were considered to be statistically significant.

RESULTS

Study population

From the original number of 2,380 subjects without a history of diabetes, 102 individuals (4.3%) were excluded from the analysis because of missing information on more than one stressful event. A total of 16 other subjects had missing OGTT data. The remaining 2,262 subjects did not show important differences in sex and age distribution compared with the original sample. Prevalence of undetected diabetes also was unaffected (data not shown). Table 2 shows the characteristics of the study population by number of nonwork stressful events. By focusing on potential confounding variables, we found that only age and sex were significantly associated with the number of nonwork stressful events (Table 2).

Distribution of life events

Life events not related to work (maximum of 10) (Table 2) were studied for all participants (*n* = 2,262). We found no events in 21.3% of subjects, one event in 36.3%, two events in 24.7%, three events in 10.7%, four events in 4.5%, five events in 1.8%, six events in 0.6%, and seven events in 0.2%. The latter four categories were combined into four or more events (*n* = 161, 7.1%) to have enough cases to evaluate undetected diabetes prevalence. Missing information on a single event occurred in 20 cases (0.8%). The question concerning conflict with a partner was the most frequently unanswered question (six cases).

Work-related life events were scored only among the participants with salaried jobs for the past 5 years (*n* = 860). A total of 370 subjects reported at least one work-related life event (43%) in 205 cases pertaining to retirement from work.

Association of major stressful life events with undetected type 2 diabetes

In the total population of 2,262 subjects, 112 participants had previously undetected diabetes (5.0%). Regarding single nonwork stressful events, experiencing the death of a partner or moving from a house corresponded to a significantly higher percentage of undetected diabetes (10.6 and 6.9%, respectively) (Table 1). The association with death of a relative was of borderline significance. The latter three events were not mutually associated.

Among subjects with a salaried job for the past 5 years (*n* = 860), the age- and sex-adjusted prevalence of undetected diabetes was 3.1%. None of the single events was associated with the prevalence of undetected diabetes (Table 1).

Next, we counted the total number of stressful events experienced during the past 5 years for each participant. Concerning the nonwork events, we found that the more events reported, the higher the prevalence of previously undetected diabetes (Table 3). The odds ratio (OR) for the difference of one event adjusted for age and sex was 1.2 (95% CI 1.1–2.5; $P < 0.05$).

In addition, we compared subjects with the highest number of stressful events (three or more stressful life events, *n* = 402) with the remaining subjects (less than three events, *n* = 1,860), which implied contrasting the highest quintile with the rest of the population. The age- and sex-adjusted OR was 1.6 (1.0–2.6) ($P < 0.05$). This association with undetected diabetes remained statistically significant after additionally adjusting for family history of diabetes, physical activity, heavy alcohol consumption (>30 g/day), and low level of education (yes/no) (1.7 [1.0–2.7]) ($P < 0.05$).

Table 3—*Prevalence of undetected type 2 diabetes by number of nonwork stressful life events in a white population aged 50–74 years (*n = *2,262)*

	Number of nonwork stressful life events during the past 5 years (maximum = 10)				
	0	1	2	3	≥4
Events (*n*)	482	820	558	241	161
Diabetes*	19 (4.5)	35 (4.3)	28 (4.8)	18 (7.1)	12 (7.4)

Data are *n* or *n* (%). *Prevalence data adjusted for age and sex by analysis of covariance.

In the subgroup of working participants (n = 860), the number of work-related events was not related to undetected diabetes prevalence (data not shown).

Association of major stressful life events with WHR

The average (mean ± SD) WHR in our study population was 0.95 ± 0.06 for men and 0.84 ± 0.07 for women. These values can be considered reference values in a middle-aged white population without a history of diabetes. Table 2 shows that the more nonwork stressful events reported, the higher the WHR. In men, the WHR ranged from 0.94 to 0.96, and in women it ranged from 0.84 to 0.85. Although these differences were small, the association between number of stressful events (independent variable) and WHR (dependent variable) was statistically significant (Table 2). The association of stress with fasting insulin (another potential intermediate between stress and diabetes) was not significant (Table 2). Dichotomizing the insulin variable (in the highest quintile, yes/no) also did not result in a significant association with the stress variable (data not shown).

Potential intermediary role of WHR

After adding the WHR as a covariate to the logistical regression model (having undetected diabetes as the dependent variable and number of life events [three or more events = 1 and less than three events = 0], age, and sex as independent variables), the association between stress and diabetes was only marginally reduced. The OR changed from 1.6 (1.0–2.6) ($P < 0.05$) to 1.5 (0.9–2.4) ($P = 0.08$).

CONCLUSIONS — Because of the cross-sectional design of this study, the association between stress and diabetes can be interpreted in three ways: *1*) the experience of life events is one of the causal factors for type 2 diabetes; *2*) type 2 diabetes is one of the causal factors of traumatic life events; *3*) both factors are *not* causally related: a third underlying factor explains the association between the two factors. As stated previously, the second interpretation is improbable because the subjects were not aware that they had diabetes. As for the third interpretation, low socioeconomic status could be an underlying factor (15). However, the association between our stress indicator and diabetes was not affected by level of education (an indicator for socioeconomic status).

How plausible is the first interpretation? Does the adverse effect of the major life events last long enough to contribute to an impairment of glucose tolerance? In general, the length of the pre-illness period is likely to vary between individuals, depending on the number of present risk factors for diabetes. This time frame and the effect of the various risk factors, including stress, on glucose tolerance can only be studied in longitudinal studies. Our study population is not a selected high-risk population but an aselect sample from the general population without a history of diabetes. For this population, it has to be assumed that the insult on insulin sensitivity and/or β-cell function must have been long lasting to affect glucose tolerance. This is the kind of stress effect that we usually associate with major life events as defined in this study. For example, very few individuals will recover from the death of a loved one within weeks, even if they have high coping ability or enjoy strong social support. Some of our questions actually included the expression "long-lasting problems." Thus, major life events may well contribute to the onset of diabetes, at least in individuals already at risk for diabetes.

We did not find an association between work-related events and type 2 diabetes. The face validity of the work-related events as the origin of psychological stress is less compelling. The emotional effect of at least three of the work-related events (retirement, disability, forced job change) may vary from individual to individual and may be further mitigated by the social security system in the Netherlands.

An important finding was that, in our white middle-aged population, the accumulation of visceral fat did not seem to be the major mediating factor between stress and diabetes. Fasting insulin concentration, which is an approximation of insulin resistance (16), was also not higher in individuals who had experienced more events. This raises the question of whether other more classical mediating factors (such as chronic stimulation of adrenergic activity with resulting hyperglycemia) constitute a more important link (17,18).

In conclusion, our results partially support Björntorp's theory. A high number of rather common major life events that probably indicate chronic psychological stress during the past 5 years was indeed related to a higher prevalence of previously unknown type 2 diabetes. This association was independent of family history of diabetes, physical activity, heavy alcohol use, or low level of education. Also corresponding with this theory was the fact that our psychological stress indicator was positively associated with the WHR, which indicates increased levels of visceral fat. However, this association was weak, and the WHR was clearly not the main mediating factor in the association between psychological stress and type 2 diabetes.

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