

Simple self-reported behavioral or psychological characteristics as risk factors for future type 2 diabetes in Japanese individuals: Toranomon Hospital Health Management Center Study 14

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ABSTRACT

Aims/Introduction: Depression, anger, sleep disorders and cognitive impairment are regarded as presenting a high risk for diabetes. We investigated whether responses to single statements on a self-report questionnaire on the presence of each of these four factors were associated with the development of type 2 diabetes.

Materials and Methods: We investigated 3,211 Japanese individuals without diabetes. Cumulative incidence rate and hazard ratios (HRs) for future type 2 diabetes over 7–13 years were evaluated according to the presence of lack of perseverance, anger, memory loss or sleep disorders.

Results: Results of Cox regression analysis showed that lack of perseverance (age- and sex-adjusted HR 1.41, 95% confidence interval 1.07–1.84), anger, (HR 1.51, 95% confidence interval 1.07–2.12) or memory loss (HR 1.47, 95% confidence interval 1.14–1.90) was predictive of the development of diabetes. Even after adjustment for metabolic factors including glycemic measurements, anger was significantly associated with an increased risk of future diabetes. Individuals with both anger and memory loss had a 1.94-fold (95% confidence interval 1.19–3.15) increased risk of type 2 diabetes than those without those two symptoms.

Conclusions: Responses to a simple self-report questionnaire as to whether individuals were aware of anger or memory loss were associated with the development of type 2 diabetes independent of traditional risk factors for diabetes in this cohort of Japanese individuals.

INTRODUCTION

Behavioral symptoms or psychological stress assessed by time-consuming objective questionnaires were reported to be associated with the occurrence of diabetes. Among these, reviews and results of meta-analyses have suggested a strong association of diabetes with depression^{1,2} or with cognitive impairment^{3,4}. In addition, roles of general emotional stress, sleep problems,

anger and hostility as risk factors for the development of type 2 diabetes were also suggested⁵. A meta-analysis showed that quantity and quality of sleep, including difficulty in initiating sleep and difficulty in maintaining sleep, were associated with an increased future diabetes risk⁶. A longitudinal study reported that anger, hostility and type A characteristics, but not severity of symptoms of depression, significantly predicted higher fasting glucose concentrations among older men over a period of 9 years⁷. Results of the Atherosclerosis Risk in Communities

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Study also suggested that an angry temperament was modestly associated with the development of future type 2 diabetes⁸. In results of cross-sectional studies, characteristics of hostility were associated with insulin sensitivity⁹, and individuals with high stress and high hostility were more likely to have insulin resistance¹⁰.

Although these behavioral symptoms or psychological stresses can be considered as novel markers for risk of future diabetes, whether responses to simple statements on the presence of one or more of such factors would be effective in screening individuals at high risk of type 2 diabetes remains uncertain. In addition to traditional risk factors for the development of type 2 diabetes, including glycemic markers, negative stress factors that could be assessed by a self-report questionnaire might be possible predictors of the development of diabetes. We therefore tested the hypotheses that: (i) a simple self-report questionnaire on negative behavioral or psychological characteristics including perseverance, anger, memory loss or sleep disorders would be predictive of the development of type 2 diabetes; and (ii) that the association would be independent of metabolic factors including glycemic measurements in Japanese individuals.

MATERIALS AND METHODS

Study Participants

The Toranomon Hospital Health Management Center Study (TOPICS) mainly included apparently healthy government employees who underwent annual health examinations for health screening in addition to some members of the general public in Tokyo, Japan. Routine health check-ups are very common in Japan, because the Japanese government and companies encourage people to have periodic health examinations¹¹. We retrospectively examined data on 3,418 individuals who underwent health examinations on an annual basis during a 7- to 13-year follow-up period from 1997 to 2005 at the center. We excluded individuals who had diabetes at the baseline examination ($n = 151$) or with missing data on baseline characteristics ($n = 61$). Subsequently, 3,211 individuals (2,371 men and 840 women) aged 25–80 y (mean 49.5 years, standard deviation 9.0 years) were eligible for the current analysis. Diagnosis of type 2 diabetes was made according to the American Diabetes Association criteria¹² of fasting plasma glucose (FPG) level ≥ 7.0 mmol/L, self-reported clinician-diagnosed diabetes or glycated hemoglobin (HbA1c) ≥ 48 mmol/mol ($\geq 6.5\%$). The study protocol followed the Japanese Government's Ethical Guidelines Regarding Epidemiological Studies in accordance with the Declaration of Helsinki, and was reviewed by the institutional review board at Toranomon Hospital.

Assessment of Self-Report of Behavioral or Psychological Symptoms

At the baseline examination, behavioral or psychological factors were assessed using a questionnaire. We used a one-item approach, and it was determined whether or not individuals

gave a positive answer to items on lack of perseverance, anger (testy, or easily annoyed), memory loss or sleep disorder. The four statements were 'I do not persevere with tasks,' 'I am easily moved to anger,' 'I am experiencing memory loss' or 'I have difficulty in falling asleep or staying asleep'.

Clinical Measurements

Anthropometric measurements, such as those of bodyweight and height, were carried out during the baseline examination by trained staff. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Hospital staff measured blood pressure with the individual in a sitting position. Blood samples were collected after an overnight fast (12 h), and measurements were made using an automatic clinical chemistry analyzer (LABOSPECT 008; Hitachi, Tokyo, Japan). Blood glucose, serum triglycerides and high-density lipoprotein cholesterol concentrations were measured by enzymatic methods. HbA1c was assessed by high-performance liquid chromatography. The value for HbA1c (%) was estimated as the National Glycohemoglobin Standardization Program value (%) calculated by the formula $\text{HbA1c} (\%) = \text{HbA1c (Japan Diabetes Society; \%)} \times 1.02 + 0.25\%^{13}$.

Statistical Analysis

Cox regression model was carried out to estimate hazard ratios (HRs) and their 95% confidence intervals (CIs) for the development of type 2 diabetes. Follow-up time for each participant was calculated from the date of the initial screening examination to the date of confirmed diabetes or the date of the last follow-up examination. We carried out the following multivariate analysis including age, sex, parental history of diabetes, BMI, smoking habit (never, former and current), physical activity habit, hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or medical treatment), log-transformed triglycerides and high-density lipoprotein cholesterol. We then added FPG (multivariate + FPG model) or FPG and HbA1c (multivariate model + FPG and HbA1c model) into the model. Analysis was carried out with IBM SPSS Statistics version 19 (IBM, Armonk, NY, USA). Statistical significance was considered for $P < 0.05$.

RESULTS

During the follow-up time of 31,242 person-years, 347 individuals developed type 2 diabetes. Table 1 shows the characteristics of the study participants at the baseline examination who did or did not develop diabetes. Compared with individuals who did not develop diabetes, those who developed diabetes were more likely to be older, male, former or current smokers, have a history of parental diabetes, have elevated values for BMI, triglycerides, FPG and HbA1c or low values for high-density lipoprotein cholesterol at the baseline examination. We observed that a greater percentage of individuals who developed diabetes had a positive answer for lack of perseverance (χ^2 -test, $P = 0.030$), anger ($P = 0.064$), memory loss ($P = 0.007$) or

Table 1 | Baseline characteristics of study participants according to incidence of type 2 diabetes during the follow-up period of 7–13 years

| | Non-diabetics (<i>n</i> = 2864) | Diabetes (<i>n</i> = 347) | <i>P</i> -value |
|---|-------------------------------------|-------------------------------|-----------------|
| Age (years) | 49.2 (9.0) | 51.6 (8.2) | <0.001 |
| Women | 795 (27.8) | 45 (13.0) | <0.001 |
| Parental history of diabetes | 373 (13.0) | 74 (21.3) | <0.001 |
| Body mass index (kg/m ²) | 22.6 (2.8) | 23.9 (3.1) | <0.001 |
| Smoking habit | | | <0.001 |
| Never | 1659 (57.9) | 150 (43.2) | – |
| Former | 668 (23.3) | 96 (27.7) | – |
| Current | 537 (18.8) | 101 (29.1) | – |
| Physical activity habit (yes) | 1458 (50.9) | 169 (48.7) | 0.438 |
| Hypertension* | 557 (19.4) | 103 (29.7) | <0.001 |
| Triglycerides (mmol/L) | 1.02 (0.73, 1.48) | 1.39 (0.94, 2.05) | <0.001 |
| HDL cholesterol (mmol/L) | 1.43 (0.38) | 1.29 (0.39) | <0.001 |
| Fasting plasma glucose (mmol/L) | 5.2 (0.4) | 5.8 (0.5) | <0.001 |
| HbA1c (%) | 5.2 (0.3) | 5.6 (0.4) | <0.001 |
| HbA1c (mmol/mol) | 33 (3) | 38 (4) | <0.001 |
| Lack of perseverance (yes) | 411 (14.4) | 65 (18.7) | 0.030 |
| Anger (yes) | 223 (7.8) | 37 (10.7) | 0.064 |
| Memory loss (yes) | 449 (15.7) | 74 (21.3) | 0.007 |
| Sleep disorders (yes) | 392 (13.7) | 57 (16.4) | 0.165 |

Data are *n* (%), means (standard deviation) or median (interquartile ranges) unless otherwise indicated. Categorical data were analyzed using the χ^2 -test. *P*-values between non-diabetics and diabetes were tested by *t*-test or median test. *Hypertension is defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or treatment. HbA1c, glycated hemoglobin; HDL, high-density lipoprotein.

sleep disorders (*P* = 0.165) than those who had not developed diabetes. In comparisons of differences in FPG and HbA1c concentrations between individuals with and without the

presence of each behavioral or psychological characteristic using the *t*-test (details of data not shown), we did not observe statistically significant differences (*P* < 0.05). When we assessed differences in the characteristics of participants according to the presence or absence of each of the four factors, there was an overlap between the symptoms; for example, of the individuals with anger (*n* = 260), 43.5% (*n* = 113) also had lack of perseverance, 42.7% (*n* = 111) had memory loss and 25.0% (*n* = 65) had sleep disorders (Supplemental Table S1).

Results of Cox regression analysis (age- and sex-adjusted model) showed that individuals with lack of perseverance (HR 1.41, 95% CI 1.07–1.84), memory loss (HR 1.47, (95% CI 1.14–1.90) or anger (HR 1.51, 95% CI 1.07–2.12) had a significantly increased risk of the development of type 2 diabetes (Table 2). Even after adjustment for traditional risk factors for type 2 diabetes, including metabolic factors, FPG and HbA1c, a positive answer on anger was strongly associated with a 1.70-fold (95% CI 1.20–2.40) higher HR for type 2 diabetes (multivariate + FPG and HbA1c model) compared with those without a positive response for anger. Memory loss was associated with a HR 1.27 (95% CI 0.97–1.65, *P* = 0.078) for type 2 diabetes (multivariate + FPG and HbA1c model). Results of Kaplan–Meier analysis (Figure 1) showed that the cumulative incidence rate of type 2 diabetes was modestly elevated over the 7–13 years follow-up time among individuals with anger (A; log-rank test, *P* = 0.038) or memory loss (B; *P* = 0.004) compared with those who did not report such a symptom.

We further assessed whether the combination of the two symptoms additively influenced an increase in the risk of the development of type 2 diabetes. Compared with individuals without the presence of these two factors (Figure 2; group a), those with both anger and memory loss had the highest cumulative incidence rate of type 2 diabetes (Figure 2; group d). Results of Cox regression analysis showed that individuals with both anger and memory loss had a HR of 1.94 (95% CI 1.19–3.15) for the development of type 2 diabetes compared with those without the two factors, even after adjustment for FPG, HbA1c and other metabolic factors (Table 3; multivariate + FPG and HbA1c model).

Table 2 | Hazard ratios for the development of type 2 diabetes by a self-report questionnaire on behavioral or psychological characteristics

| | Cases/total person-years | Unadjusted HR (95% CI) | Age- and sex-adjusted HR | Multivariate- adjusted HR* | Multivariate + FPG-adjusted HR | Multivariate + FPG and HbA1c- adjusted HR |
|--|-----------------------------|---------------------------|-----------------------------|-------------------------------|-----------------------------------|---|
| Lack of perseverance (<i>n</i> = 476) | 65/4,553 | 1.36 (1.04–1.78) | 1.41 (1.07–1.84) | 1.32 (1.01–1.73) | 1.09 (0.83–1.44) | 1.09 (0.83–1.43) |
| Sleep disorders (<i>n</i> = 449) | 57/4,264 | 1.25 (0.94–1.66) | 1.27 (0.95–1.69) | 1.32 (0.99–1.75) | 1.20 (0.90–1.59) | 1.21 (0.91–1.61) |
| Memory loss (<i>n</i> = 523) | 74/4,916 | 1.46 (1.13–1.89) | 1.47 (1.14–1.90) | 1.37 (1.06–1.78) | 1.28 (0.98–1.66) | 1.27 (0.97–1.65) |
| Anger (<i>n</i> = 260) | 37/2,421 | 1.43 (1.02–2.01) | 1.51 (1.07–2.12) | 1.49 (1.06–2.10) | 1.63 (1.16–2.31) | 1.70 (1.20–2.40) |

*Multivariate model included age, sex, parental history of diabetes, body mass index, smoking habit (never, former, current), physical activity habit, hypertension, log-transformed triglycerides and high-density lipoprotein cholesterol. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HR, hazard ratio.

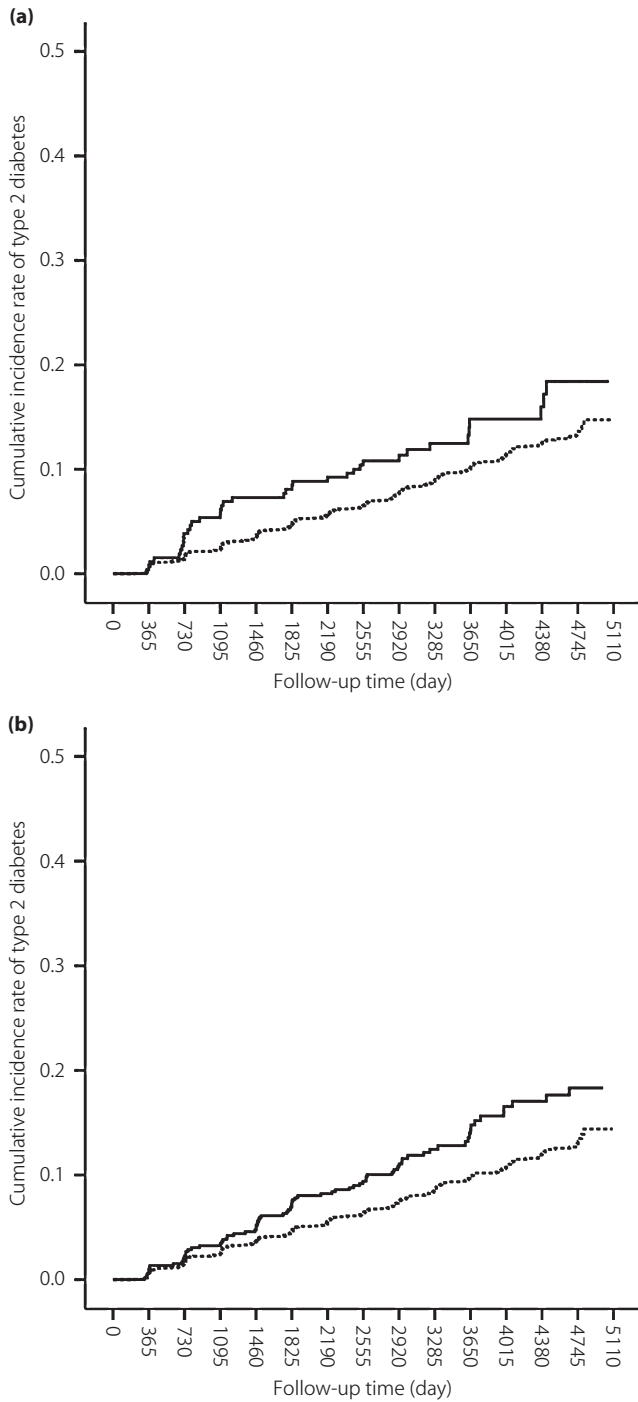


Figure 1 | Cumulative incidence rate of type 2 diabetes according to (a) anger and (b) memory loss in Japanese individuals. Solid line: individuals with the characteristic; dotted line: others.

DISCUSSION

In the present study of apparently healthy Japanese individuals, we observed that a positive response to whether an individual experienced anger or memory loss was predictive of future type 2 diabetes independent of metabolic factors. We found

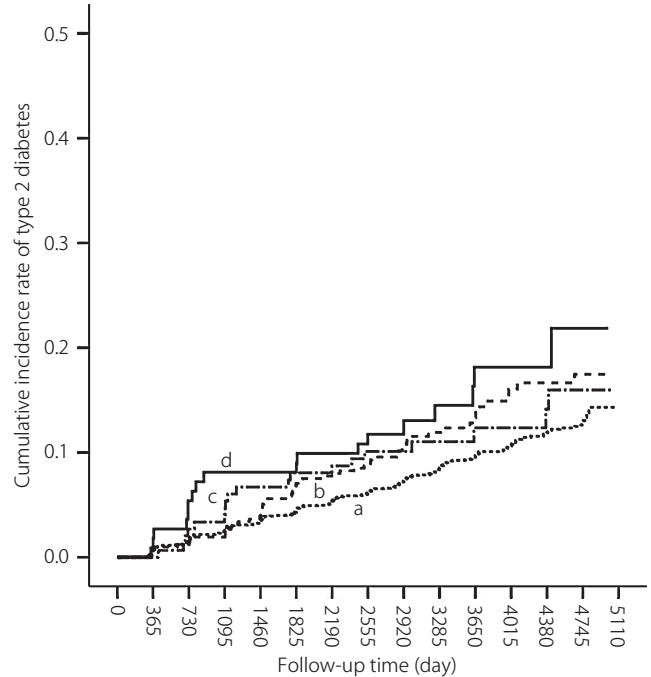


Figure 2 | Combined effect of self-reported anger and memory loss on the incidence rate of type 2 diabetes in Japanese individuals. Group a, without anger and memory loss; group b, memory loss alone; group c, anger alone; group d, both anger and memory loss.

that risk of the development of type 2 diabetes was particularly elevated among individuals who responded positively to both items compared with those who did not.

Among the four factors that we examined in the present study, anger was the most strongly associated with the development of type 2 diabetes in Japanese men and women, and we observed that a person with anger was more likely also to have other symptoms. A few studies have prospectively investigated anger and risk of the development of type 2 diabetes^{7,8}. In a prospective investigation as part of the Atherosclerosis Risk in Communities Study, an angry temperament was modestly associated with the development of type 2 diabetes, although this association was not independent of obesity and blood measurements⁸. According to the results of the Veterans Affairs Normative Aging Study, hostility, anger and type A behavior were considered as risk factors for impaired glucose metabolism among unmarried older men⁷. Although we cannot determine the mechanisms for our results from the present observational study, according to the results of other studies, different pathways could be considered for the association of anger and impaired glucose metabolism. Chronic stress induces activation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. Long-term activation of the hypothalamic–pituitary–adrenal axis increases catecholamine and cortisol release, which might induce impaired glucose metabolism⁹ and visceral fat accumulation¹⁴, which could increase the risk of the development of type 2 diabetes. It was reported that a higher result in the Cook–Medley Hostility scale

Table 3 | Hazard ratios and 95% confidence intervals for the development of type 2 diabetes by a combination of responses on the presence of memory loss or anger

| | Group a: Without anger and memory loss | Group b: Memory loss alone | Group c: Anger alone | Group d: Both anger and memory loss |
|--|--|----------------------------|----------------------|-------------------------------------|
| <i>n</i> | 2539 | 412 | 149 | 111 |
| Cases/total person-years | 254/24905 | 56/3916 | 19/1421 | 18/1000 |
| Unadjusted HR | 1.00 (Ref.) | 1.41 (1.05–1.88) | 1.32 (0.83–2.10) | 1.79 (1.11–2.89) |
| Age- and sex-adjusted HR | 1.00 (Ref.) | 1.42 (1.06–1.90) | 1.43 (0.90–2.29) | 1.80 (1.12–2.91) |
| Multivariate adjusted HR* | 1.00 (Ref.) | 1.30 (0.97–1.74) | 1.35 (0.85–2.16) | 1.84 (1.14–2.98) |
| Multivariate + FPG adjusted HR | 1.00 (Ref.) | 1.17 (0.87–1.57) | 1.45 (0.91–2.33) | 2.00 (1.23–3.24) |
| Multivariate + FPG and HbA1c adjusted HR | 1.00 (Ref.) | 1.17 (0.87–1.58) | 1.59 (0.99–2.55) | 1.94 (1.19–3.15) |

*Multivariate model included age, sex, parental history of diabetes, body mass index, smoking habit (never, former, current), physical activity habit, hypertension, log-transformed triglycerides and high-density lipoprotein cholesterol. CI, confidence interval; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HR, hazard ratio.

in combination with higher norepinephrine values was associated with greater insulin resistance¹⁰. It was also reported that there were associations with unhealthy lifestyle behaviors, such as smoking and physical inactivity, in individuals with high levels of stress¹⁵. As we could not consider differences in nutritional intake and the degree of physical activity among participants, we cannot deny the possibility that these factors might have influenced our observations.

Also, evidence has shown that type 2 diabetes is strongly associated with cognitive impairment^{3,4,16,17}. According to a review article, although not conclusively, it was shown that people with type 2 diabetes might perform worse than healthy controls on learning and memory tests⁴, although further investigations are currently ongoing. That modest cognitive decrements were already present at the early stage of type 2 diabetes was also suggested.¹⁸ In a recent cross-sectional study of healthy middle-aged people, poor cognitive performance was associated with adiposity and high (but still normal) HbA1c levels¹⁹. The etiology of cognitive dysfunction in patients with type 2 diabetes is considered to be multifactorial³, and chronic hyperglycemia and a long duration of diabetes would both be associated with increased development of cognitive dysfunction, as is the presence of cardiovascular risk factors including hypertension, hypercholesterolemia and obesity^{3,4}. Nevertheless, the association of self-reported memory loss and elevated future type 2 diabetes risk was independent of the metabolic factors of BMI, hypertension and lipid measurements.

Although the diagnosis of an angry temperament, memory disturbances and symptoms of stress through assessment instruments is most optimally made by several questions regarding each factor, in the present study we only used one item to assess each factor in the self-reported questionnaire. Therefore, our approach is not adequate for accurately assessing the degrees of these characteristics in comparison with the more extensive objective questionnaires that are usually used in epidemiological studies. Although the use of a single question would be inadequate for the assessment of each symptom, there has been an attempt to compare the one-question or one-item

approach with a recommended objective approach for screening of psychological stress²⁰. The present results showed that further attention should be paid to the presence of these stress symptoms as risk factors for the development of diabetes in routine care settings. Further research should investigate the impact of degrees of psychological stress on the subsequent risk of the development of type 2 diabetes using validated questionnaires to confirm the present findings. Whether using a simple tool would be a quick alternative to introducing time-consuming questionnaires or assessment instruments in predicting risk of future type 2 diabetes should be further investigated in other study populations. As we observed that unfavorable symptoms overlapped, healthcare professionals would need to give attention to whether a patient with anger would have other symptoms, such as memory loss or depression, which are also known risk factors for the development of diabetes^{1,2}.

A strength of the present study was the long-term follow-up period. Several limitations should be considered in this study. We did not validate the items in our assessment based on how the responses to our questions were positively associated with scores of other objective instruments for the assessment of psychological stress. Also, the prediction of type 2 diabetes was carried out using data on symptoms assessed only at the baseline examination, and some participants might not have a particular symptom consistently during the study period. We did not have detailed data on dietary habits¹⁵ and inflammation²¹, which were considered to be mediating factors for the association of these behavioral or stress symptoms and type 2 diabetes. As our cohort consisted of individuals who had annual health check-ups, generalizability of the present results should be investigated in other populations. Also, our study participants mainly consisted of males, and it was difficult to carry out a sex-stratified analysis because of the limited number of female study participants. Studies examining sex differences in behavioral or psychological characteristics and the risk of developing type 2 diabetes are required.

In conclusion, we observed that positive responses to simple items on anger and memory loss were associated with a long-

term risk of the development of type 2 diabetes in this cohort of Japanese individuals. The associations that we identified as placing individuals at risk of type 2 diabetes were independent of the traditional risk factors. Further studies of different populations would be required to confirm our findings, and to clarify whether using a simple questionnaire rather than a time-consuming questionnaire would be effective for predicting the risk of the development of diabetes in other populations.

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SUPPORTING INFORMATION

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

Table S1 Characteristics of study participants according to the absence or presence of (1) lack of perseverance, (2) anger, (3) memory loss and (4) sleep disorders at the baseline examination.