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Running title: Psychological distress and type 2 diabetes

Psychological Distress and Incidence of Type 2 Diabetes in High-Risk and Low-Risk Populations: The Whitehall II Cohort Study

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ABSTRACT

OBJECTIVE—We examined whether psychological distress predicts incident type 2 diabetes and if the association differs between populations at higher or lower risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS—Prospective cohort of 5,932 diabetes-free adults (4,189 men, 1,743 women, mean age 54.6 years) with three 5-year data cycles (1991-2009), a total of 13,207 person-observations. Participants were classified into 4 groups according to their prediabetes status and Framingham Offspring Type 2 Diabetes Risk Score: normoglycemia with a risk score of 0-9; normoglycemia with a risk score of 10-19; prediabetes with a risk score of 10-19; prediabetes with a risk score of >19. Psychological distress was assessed by the General Health Questionnaire. Incident type 2 diabetes was ascertained by 2-hour oral glucose tolerance test, doctor diagnosis or use of antihyperglycemic medication at the 5-year follow-up for each data cycle. Adjustments were made for age, sex, ethnicity, socioeconomic status, antidepressant use, smoking, and physical activity.

RESULTS—Among participants with normoglycemia and among those with prediabetes combined with a low risk score, psychological distress did not predict type 2 diabetes. Diabetes incidence in these groups varied between 1.6% and 15.6%. Among participants with prediabetes and a high risk score, 40.9% of those with psychological distress compared with 28.5% of those without distress developed diabetes during the follow-up. The corresponding adjusted odds ratio for psychological distress was 2.07 (95% CI 1.19-3.62).

CONCLUSIONS— These data suggest that psychological distress is associated with an accelerated progression to manifest diabetes in a sub-population with advanced prediabetes.

Type 2 diabetes is preceded by a period of marked changes in glucose regulation. The pre-diabetic period can last over 10 years (1) providing a crucial window for effective prevention of type 2 diabetes. To date, the focus of preventive efforts has been on lifestyle and pharmacological interventions (1-3). However, there has been widespread interest in the role of psychological factors, such as depression and stress, in the onset of type 2 diabetes. Suggested plausible mechanisms are health risk behaviors and increased body weight, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis, overactivation of the sympathetic nervous system and increased chronic inflammation; all of which are known to adversely affect glucose metabolism (4, 5).

There is some evidence that depression is an independent risk factor for type 2 diabetes (6-8), but findings for 'general' stress and work stress are less consistent (9-18). A major limitation of existing research on psychological factors and diabetes risk is reliance on the crude dichotomization; no diabetes versus diabetes. This categorization does not take into account the long prediabetic period preceding manifest disease and the possibility that those at an advanced stage on the continuum between health and disease might be differentially vulnerable to the effects of psychological factors (17). Some evidence to support this hypothesis was found in a study including 128 male Japanese workers with prediabetes which reported an increased risk of type 2 diabetes among those with high levels of baseline stress (19).

Although it captures a range of comorbid psychological factors, such as depressive and anxiety symptoms, stress and disturbed sleep, psychological distress has rarely been examined as a psychological risk factor for type 2 diabetes (11, 18, 20) and no study has examined whether the associations differ in populations at higher or lower risk of progressing to manifest diabetes. In this study we examined whether psychological distress at baseline differentially predicted incident type 2 diabetes in analyses stratified by the type 2 diabetes risk level based on (1) the presence or absence of prediabetes and (2) on the Framingham Offspring type 2 diabetes risk score (21).

RESEARCH DESIGN AND METHODS

Participants and procedure

Recruitment to the Whitehall II study took place between 1985 and 1988 among all office staff, aged 35 to 55 years, in 20 London-based Civil Service departments (22). The response rate was 73% (6,895 men and 3,413 women). Informed consent was obtained from all participants and University College London Medical School Committee on the Ethics of Human Research approved the protocol.

The target population for the present study was a sample of 5,932 participants (4,189 men, 1,743 women, mean age 54.6 years) for whom data were collected in at least 2 of the following cycles: from 1991-3 to 1997-9, from 1997-9 to 2002-4, and from 2002-4 to 2007-9. Included participants had complete data on type 2 diabetes, psychological distress, Framingham Offspring type 2 diabetes risk score (21) and covariates (age, sex, socioeconomic status, ethnicity, antidepressant use, smoking, and physical activity) at baseline. Those included in the analyses were free of diabetes at the baseline cycle(s) and had data on their pre-diabetes status and Framingham Offspring type 2 diabetes risk score (Figure 1). Each participant could thus contribute to a minimum of 1 and a maximum of 3 cycles. The 5,932 eligible participants produced 13,207 person-observations, mean follow-up time between baseline and follow-up for each cycle was 5.46 (SD=0.51) years.

Ascertainment of type 2 diabetes, prediabetes and type 2 diabetes risk status

At each clinical phase venous blood samples were taken from individuals who were fasting ≥ 8 hours (those whose clinic visit was in the afternoon had a light fat-free breakfast and they were

asked to fast for ≥ 5 hours) before undergoing a standard 2-h 75g oral glucose tolerance test (1). Diabetes was defined as fasting glucose ≥ 7.0 mmol/L, 2-hour post-load glucose ≥ 11.1 mmol/L (23-26), self-reported doctor-diagnosed diabetes, or use of diabetes medication. Blood samples were handled at all phases using similar standard protocols, and baseline cases were excluded from the prospective analyses. Prediabetes was defined as impaired fasting glucose (IFG, a fasting glucose of 5.6-6.9 mmol/L and 2-hour glucose < 7.8 mmol/L) and/or impaired glucose tolerance (IGT, a fasting glucose < 7 mmol/L and a 2-hour post-load glucose of 7.8-11.0 mmol/L) (23).

The Framingham Offspring Type 2 Diabetes Risk Score is based on a previously published detailed algorithm (21) with the following components: impaired fasting glucose (IFG), overweight or obesity, low level of high-density lipoprotein (HDL), high level of triglycerides, elevated blood pressure or antihypertensive medication, and parental diabetes. The total score ranges from 0 to 30. In the present analysis, participants with impaired glucose tolerance (IGT) received the same score as those with IFG (10 points in both cases). In the Framingham Offspring study, participants with > 19 points had an 8-year incidence of type 2 diabetes $> 15\%$ (21), thus we used this score to determine high risk status. Participants with normoglycemia scored 0 to 18 in the Framingham risk score and were further classified into the low risk group (0-9 points) and intermediate risk group (10-19), the latter range corresponding to the lower (i.e., intermediate) risk group (10-19 points) among participants with prediabetes. Based on the baseline information on prediabetes status and the Framingham risk score, participants were classified into four groups: 1) no prediabetes, low Framingham risk score (0-9); 2) no prediabetes, intermediate Framingham risk score (10-19); 3) prediabetes with intermediate Framingham risk score (10-19); and 4) prediabetes with high Framingham risk score (> 19).

Assessment of psychological distress

The 30-item General Health Questionnaire (GHQ-30) was used to assess psychological distress (27). The GHQ is a screening instrument designed to detect common psychological symptoms, such as depression and anxiety. It is widely used in population-based surveys and trials, and has been validated in the Whitehall II study (28). Each questionnaire item enquires about a specific symptom; response categories are scored as either 1 or 0 to indicate presence or absence of the symptom. A total score of 5 or more led to individuals being defined as GHQ-symptom 'cases' and scores 0-4 as 'non-cases' (28).

Assessment of covariates

Socio-demographic covariates included age, sex, socioeconomic status (SES; based on the last known occupational grade and divided into high, intermediate and low), and ethnicity (white, South Asian or other), are all based on survey responses (22). Antidepressant use (yes/no) and smoking (yes/no) were based on self-reported information at the baseline survey of each cycle. Physical activity was assessed at cycle 1 based on answers to questions about the frequency and duration of participation in mildly energetic (e.g., weeding, general housework, bicycle repair), moderately energetic (e.g., dancing, cycling, leisurely swimming), and vigorous physical activity (e.g., running, hard swimming, playing squash). At cycles 2 and 3, the questionnaire included 20 items on frequency and duration of participation in different physical activities (e.g., walking, cycling, sports) that were used to compute hours per week of each intensity level. Participants were classified as active (>2.5 hours/week of moderate physical activity or >1 hour/week of vigorous physical activity), inactive (<1 hour/week of moderate physical activity and <1 hour/week of vigorous physical activity), or moderately active (if not active or inactive) (29).

Statistical analysis

After harmonization of data across cycles, we examined associations between psychological distress at baseline and incident type 2 diabetes at follow-up for each cycle. We used generalized estimation equations (GEE) with a logistic link to control for intra-individual correlation between repeated measurements to estimate odds ratios (OR) and their 95% confidence intervals. GEE analysis was used because repeated measurements were nested within participants (i.e., the same individuals could contribute more than one observation to the dataset), and the GEE method takes into account non-independence of the within-participant observations when estimating standard errors. We first analyzed the association between psychological distress and the incidence of type 2 diabetes in the total cohort. Then we grouped the participants according to their baseline prediabetes status, Framingham Offspring Type 2 Diabetes Risk Score and psychological distress into 8 groups as follows: 1) normoglycemia – Framingham risk score 0 to 9 – no distress (reference group); 2) normoglycemia – score 0 to 9 – distress; 3) normoglycemia – score 10 to 19 – no distress; 4) normoglycemia – score 10 to 19 – distress; 5) prediabetes – score 10 to 19 – no distress; 6) prediabetes – score 10 to 19 – distress; 7) prediabetes – score >19 – no distress, 8) prediabetes – score >19 – distress. Models were adjusted for age, sex, SES, ethnicity, antidepressant use, smoking, and physical activity. SAS version 9.2 (SAS, Cary, NC, USA) was used for all analyses.

RESULTS

Table 1 shows the characteristics of participants at the baseline of each study cycle and in total. Proportion of participants who were white, high SES, without psychological distress, and who had incident type 2 diabetes were greater at the last cycle than at the first. Antidepressant use was more

prevalent and smoking less prevalent, and both high and low physical activity more prevalent in the latter cycles. Overall 5-year incidence for type 2 diabetes was 4.2%.

Associations between baseline covariates for participants with normoglycemia and prediabetes by psychological distress are presented in Supplemental Table S1. Irrespective of the participant's prediabetes status, psychological distress was associated with younger age, female sex, intermediate SES, non-white ethnicity, antidepressant use, smoking, and low physical activity.

In the total cohort, psychological distress did not predict type 2 diabetes after adjustment for age, sex, SES and ethnicity (OR=1.16, 95% CI 0.94-1.42, data not shown). We found no interaction between sex and psychological distress ($P=0.37$) or between ethnicity and psychological distress ($P=0.91$) in the prediction of type 2 diabetes.

We then examined whether combinations of prediabetes status, Framingham Offspring Type 2 Diabetes Risk score and psychological distress predicted the incidence of type 2 diabetes. Figure 2 shows the unadjusted incidences. Type 2 diabetes incidence was low among participants with normoglycemia and a low risk score, irrespective of the presence (1.9%) or absence (1.6%) of psychological distress. Among the normoglycemic participants with an intermediate risk score of 10-19, 7.6% of distressed and 6.0% of non-distressed people had type 2 diabetes at follow-up, the confidence intervals suggesting no association with psychological distress. Similarly, among participants with prediabetes and a Framingham risk score of 10-19, no difference was found in the incidence of type 2 diabetes between those with (15.6%) and without psychological distress (15.0%). However, among participants with prediabetes and a high Framingham risk score (>19) 40.9% of those with psychological distress developed type 2 diabetes at follow-up compared to only 28.5% of those without psychological distress.

Results of the multivariable adjusted logistic regression models confirm those from the unadjusted analysis by showing a strong dose-response association between prediabetes and Framingham risk score status, and risk of incident type 2 diabetes (Table 2). Moreover,

comparisons indicate no difference regarding the association between psychological distress and type 2 diabetes among normoglycemic participants or among those with prediabetes and a lower Framingham risk score, whereas among participants with prediabetes and a high Framingham risk score (>19), psychological distress was associated with a doubling of the risk of type 2 diabetes. A statistically significant interaction ($P=0.039$) was found when comparing the prediabetes-high Framingham risk score group with the other groups combined, as regards the association between psychological distress and incident type 2 diabetes.

The findings were replicated in sensitivity analysis using an alternative, less stringent cut-point of >18 to define high Framingham risk score (Supplemental Table S2).

CONCLUSIONS

We examined whether the association between psychological distress and incident type 2 diabetes differed between populations at different baseline risk levels of type 2 diabetes as assessed by the presence of prediabetes and the level of Framingham Offspring Diabetes Risk Score. The Framingham score is based on traditional type 2 diabetes risk factors; prediabetes, overweight or obesity, low HDL level, increased level of triglycerides, hypertension, and a history of parental diabetes. In the present study, the score was a strong predictor of incident type 2 diabetes.

Our main finding was that psychological distress is associated with a doubling of diabetes risk in high-risk populations. In the overall analysis, psychological distress was not significantly associated with type 2 diabetes. Subsequent stratified analysis revealed no association between psychological distress and type 2 diabetes in normoglycemic participants irrespective of the risk score and in participants with prediabetes and a lower Framingham risk score. However, in the group of participants with prediabetes and high risk score (>19), the 5-year incidence of diabetes was 28.5% in those without psychological distress and 40.9% in those with psychological distress at

baseline. In the multivariate adjusted model the odds ratio was twofold increased among those with psychological distress compared to those without. The findings were replicated using a lower cut-point (>18) for defining a high Framingham risk score.

Earlier literature suggests that the relationship between psychosocial factors and type 2 diabetes may be complex (16, 17). We found no overall association between psychological distress and type 2 diabetes. Earlier findings on the association between psychological factors, such as general stress and work stress, and incident type 2 diabetes have been mixed, including both null and positive findings (10-17). Inconsistencies in earlier research may not only be due to the use of different stress and distress indicators across studies but also, as our present findings suggest, a failure to recognize that the 'non-diabetes' group might be heterogeneous in terms of vulnerability to distress; those at an 'advanced' stage of prediabetes may be more affected by the adverse metabolic effects of psychological distress than those at lower risk levels (1, 17). Indeed, the effect of psychological stress factors have been suggested to be synergistic (17). Rather than a general risk factor in all diabetes-free populations, it might be a stage-specific risk factor which has a much stronger effect among those at an advanced stage of progression towards manifest type 2 diabetes. In line with our results, an earlier report from the Whitehall II study showed that work stress predicted type 2 diabetes among obese but not non-obese women (14).

Plausible pathways through which psychological distress may accelerate progression to type 2 diabetes among high-risk individuals include health risk behaviors and direct physiological pathways, such as long-term dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis leading to increased levels of glucocorticoids, especially cortisol, and changes in immune system activity leading to increased concentrations of pro-inflammatory cytokines (1, 8, 16, 17). There is some evidence supporting inflammation and lifestyle factors as mediators between depressive symptoms and incident type 2 diabetes (8).

Healthcare implications of this study include the notion that psychological distress might hamper the outcomes of intensive lifestyle and other treatment interventions targeted at high risk groups (2, 3). Psychological distress symptoms, such as stress, anxiety, depression, feelings of hopelessness and sleep disturbances have previously been shown to hinder commitment to major, long-term lifestyle changes and reduce adherence to pharmacological treatments (30).

There are limitations to our study. First, although the study had a high response rate in the successive data collection phases, loss to follow-up accumulated over time, as in most long-term cohort studies. However, large differences in missing data as a function of psychological distress and type 2 diabetes seem unlikely. Second, participants of the Whitehall II study are from an occupational cohort that is likely to cover a 'healthier' end of the variation in health status compared with the general population which limits generalizability of our findings. Third, we used the GHQ-30 to detect psychological distress symptoms. As this instrument was not designed to make a psychiatric diagnosis of depression or anxiety, we cannot exclude the possibility of confounding by unmeasured depression or anxiety disorders. However, this is unlikely to be a major source of bias because the GHQ-30 has been shown to be a valid screening instrument for mental disorders, particularly depression in the Whitehall II study (28). The strengths of this study are its large sample size and use of accurate, repeat assessments of all examined variables, use of the Framingham risk score based on clinical measurements, and ascertainment of diabetes based on the standard 75g oral glucose tolerance test at each clinical study cycle (23, 24). However, part of the incident type 2 diabetes identification was based on self-report although antihyperglycemic medication was confirmed by asking the participants to take their medications or list of medications to the study clinic. Of those participants who had self-reported diagnosis of diabetes without evidence on the use of antihyperglycemic medications (33.4% of incident cases) a substantial proportion was confirmed by a repeat OGTT or by antihyperglycemic medication at the subsequent phase leaving only 23.6% of all incident diabetes cases unconfirmed.

In summary, this observational study suggests that psychological distress may be related to accelerated progression of late stage prediabetes to clinical diabetes. Further investigations are needed to examine mechanisms linking psychological distress to onset of type 2 diabetes in this group. Current prevention guidelines do not generally consider psychological factors such as stress or depression (31), although some recognize them as contributing factors to be taken into account in efforts to prevent type 2 diabetes (32). Given the high comorbidity between psychological problems and diabetes and the accumulation of evidence on the role of psychological distress as a predictor of type 2 diabetes, it is important to consider whether more attention should be paid to psychological status among high-risk populations in addition to lifestyle modifications.

Author contributions: M.V. wrote the manuscript and researched data and, as the guarantor, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript. J.F. wrote the manuscript and reviewed/edited the manuscript. A.T. reviewed/edited the manuscript. T.A. reviewed/edited the manuscript. J.V. reviewed/edited the manuscript. A.S-M. reviewed/edited the manuscript. M.K. helped in study design, wrote the manuscript and reviewed/edited the manuscript.

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FIGURE LEGENDS

Figure 1. Flow chart of the data cycles and sample selection procedure

Figure 2. Unadjusted incidence (95 % confidence interval) of type 2 diabetes among participants with normoglycemia and participants with prediabetes; participants further stratified by the Framingham Offspring Type 2 Diabetes Risk Score (FRS) and psychological distress

	Baseline study cycle			
	All n=13,207*	1 (1991-3) n=5,331	2 (1997-9) n=3,635	3 (2002-4) n=4,241
Age; mean (SD)	54.6 (7.7)	49.2 (6.0)	55.4 (5.9)	60.6 (5.9)
Sex				
Male	9,461 (71.6)	3,788 (71.1)	2,595 (71.4)	3,078 (72.6)
Female	3,746 (28.4)	1,543 (28.9)	1,040 (28.6)	1,163 (27.4)
Ethnicity				
White	12,325 (93.3)	4,916 (92.2)	3,412 (93.9)	3,997 (94.3)
South Asian	465 (3.5)	210 (3.9)	121 (3.3)	134 (3.2)
Other	417 (3.2)	205 (3.9)	102 (2.8)	110 (2.6)
Socioeconomic status (SES)				
1 highest	5,476 (41.5)	1,841 (34.5)	1,626 (44.7)	2,009 (47.4)
2	6,120 (46.3)	2,664 (50.0)	1,610 (44.3)	1,846 (43.5)
3 lowest	1,611 (12.2)	826 (15.5)	399 (11.0)	386 (9.1)
Psychological distress				
No	10,440 (79.1)	4,173 (78.3)	2,852 (78.5)	3,415 (80.5)
Yes	2,767 (21.0)	1,158 (21.7)	783 (21.5)	826 (19.5)
Antidepressant use				
No	12,905 (97.7)	5,248 (98.4)	3,549 (97.6)	4,108 (96.9)
Yes	302 (2.3)	83 (1.6)	86 (2.4)	133 (3.1)
Smoking				
No	11,992 (90.8)	4,725 (88.6)	3,315 (91.2)	3,952 (93.2)
Yes	1,215 (9.2)	606 (11.4)	320 (8.8)	289 (6.8)
Physical activity				
High	7,392 (56.0)	2,839 (53.3)	2,033 (55.9)	2,520 (59.4)
Intermediate	2,874 (21.8)	1,542 (28.9)	603 (16.6)	729 (17.2)
Low	2,941 (22.3)	950 (17.8)	999 (27.5)	992 (23.4)

Framingham Offspring type 2 diabetes risk score; mean (SD)	5.4 (5.3)	5.0 (5.3)	5.5 (5.4)	5.8 (5.3)
Incidence of type 2 diabetes at follow-up				
No	12,657 (95.8)	5,155 (96.7)	3,482 (95.8)	4,020 (94.8)
Yes	550 (4.2)	176 (3.3)	153 (4.2)	221 (5.2)

*Total n refers to the sum of participants (n of person-observations) in total and across the three study cycles (one participant can contribute to one or more study cycle); n in each study cycle refers to number of participants at that cycle.

Table 1 - *Characteristics of the participants at the baseline of the 3 cycles. Figures are number (%) unless otherwise stated*

Prediabetes status, risk level (FRS) and psychological distress at baseline	No. of person-observations	No. of incident Cases	Odds ratio (95% confidence interval) for incident type 2 diabetes								
			Comparison 1	Comparison 2	Comparison 3	Comparison 4	Comparison 5	Comparison 6	Comparison 7	Comparison 8	
All	13,207	550									
Normoglycemia – FRS 0-9 – no distress	8,025	129	1.00 (Ref.)	0.83 (0.58-1.18)	0.27 (0.19-0.36)	0.21 (0.13-0.34)	0.10 (0.08-0.13)	0.09 (0.06-0.14)	0.05 (0.03-0.06)	0.02 (0.01-0.04)	
Normoglycemia – FRS 0-9 – distress	2,220	41	1.20 (0.84-1.71)	1.00 (Ref.)	0.32 (0.21-0.48)	0.25 (0.14-0.44)	0.12 (0.09-0.18)	0.11 (0.07-0.18)	0.06 (0.04-0.08)	0.03 (0.02-0.05)	
Normoglycemia – FRS 10-19 – no distress	1,102	66	3.77 (2.76-5.14)	3.13 (2.10-4.68)	1.00 (Ref.)	0.79 (0.47-1.33)	0.38 (0.28-0.53)	0.35 (0.23-0.56)	0.18 (0.12-0.26)	0.09 (0.05-0.15)	
Normoglycemia – FRS 10-19 – distress	263	20	4.79 (2.93-7.84)	3.98 (2.29-6.91)	1.27 (0.75-2.15)	1.00 (Ref.)	0.49 (0.30-0.80)	0.45 (0.25-0.81)	0.22 (0.13-0.38)	0.11 (0.05-0.21)	
Prediabetes – FRS 10-19 – no distress	1,043	156	9.81 (7.60-12.66)	8.15 (5.69-11.65)	2.60 (1.90-3.56)	2.05 (1.24-3.37)	1.00 (Ref.)	0.92 (0.61-1.40)	0.46 (0.33-0.63)	0.22 (0.13-0.37)	
Prediabetes – FRS 10-19 – distress	218	34	10.64 (7.03-16.11)	8.84 (5.45-14.33)	2.82 (1.79-4.44)	2.22 (1.23-4.01)	1.09 (0.72-0.64)	1.00 (Ref.)	0.50 (0.32-0.78)	0.24 (0.13-0.44)	
Prediabetes – FRS>19	270	77	21.39 (15.51-29.50)	17.77 (11.84-26.69)	5.68 (3.90-8.25)	4.47 (2.62-7.61)	2.18 (1.58-3.01)	2.01 (1.28-3.17)	1.00 (Ref.)	0.48 (0.28-0.84)	

– no distress

Prediabetes – FRS>19	66	27	44.31 (26.29-74.68)	36.81 (20.76-65.26)	11.76 (6.77-20.42)	9.25 (4.70-18.22)	4.52 (2.67-7.63)	4.16 (2.25-7.71)	2.07 (1.19-3.62)	1.00 (Ref.)
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– distress

Models are adjusted for age, sex, socioeconomic status, ethnicity, antidepressant use, smoking, and physical activity.

FRS: Framingham Offspring Type 2 Diabetes Risk Score.

*All comparisons are based on the same data, but they have a different reference group

Table 2 - Incidence of type 2 diabetes at follow-up among participants with normoglycemia and participants with prediabetes at baseline; participants further stratified by Framingham Offspring Type 2 Diabetes Risk Score (FRS) and psychological distress. Alternative reference groups are shown in comparisons 1 to 8.

Figure 1 – Flow chart of the data cycles and sample selection procedure

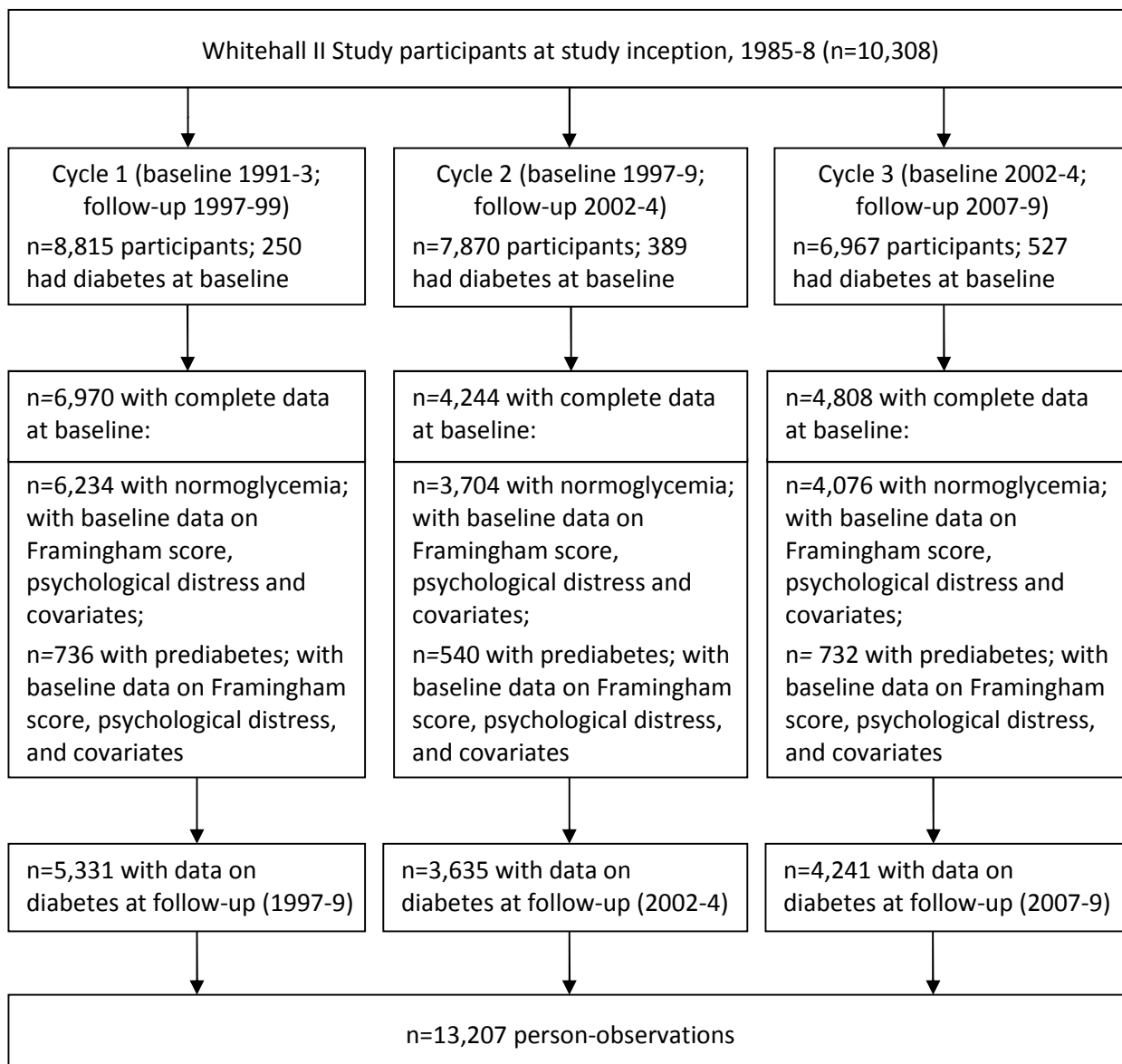
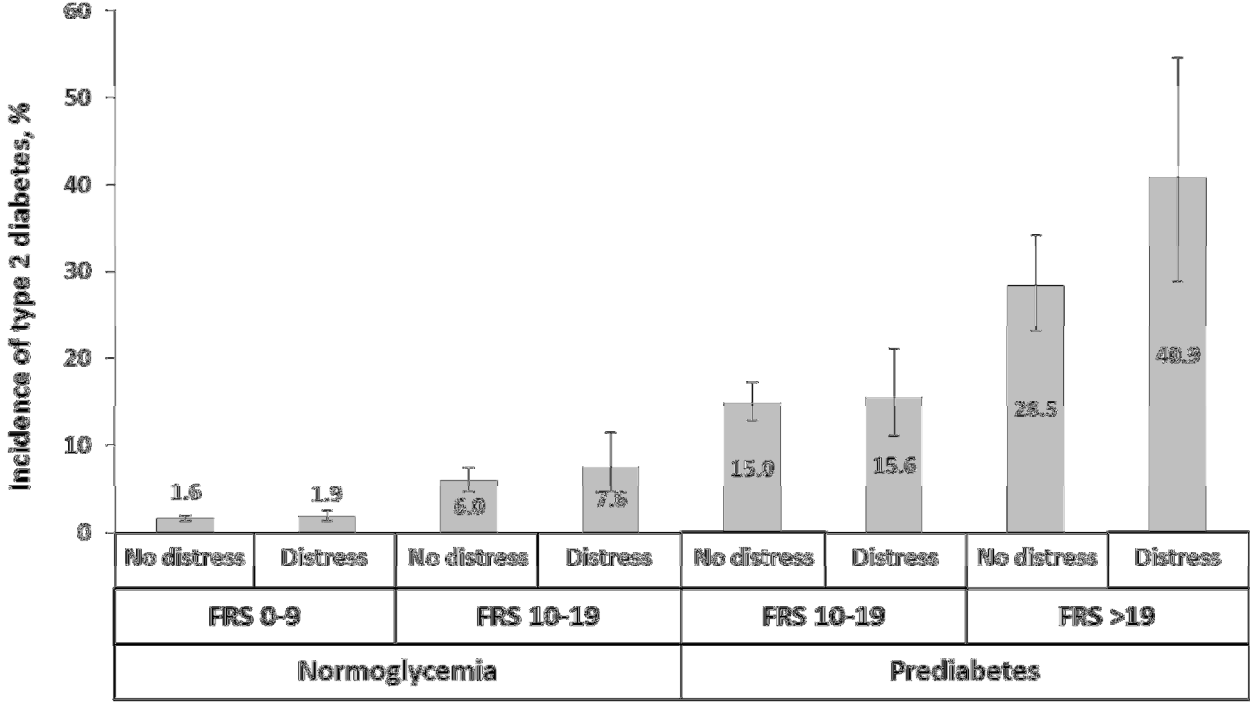


Figure 2 – Unadjusted incidence (95 % confidence interval) of type 2 diabetes among participants with normoglycemia and participants with prediabetes at baseline; participants further stratified by the Framingham Offspring Type 2 Diabetes Risk Score (FRS) and psychological distress



	Normoglycemia		Prediabetes		
	Psychological distress		Psychological distress		
	All	No	Yes	No	Yes
	n=13,207*	n=9,127*	n=2,483*	n=1,313*	n=284*
Age; mean (SD)	54.6 (7.7)	54.6 (7.7)	52.8 (7.1)	57.6 (7.6)	55.0 (7.0)
Sex					
Male	9,461 (71.6)	6,698 (73.4)	1,619 (65.2)	961 (73.2)	183 (64.4)
Female	3,746 (28.4)	2,429 (26.6)	864 (34.8)	352 (26.8)	101 (35.6)
Ethnicity					
White	12,325 (93.3)	8,562 (93.8)	2,306 (92.9)	1,201 (91.5)	256 (90.1)
South Asian	465 (3.5)	265 (2.9)	110 (4.4)	69 (5.3)	21 (7.4)
Other	417 (3.2)	300 (3.3)	67 (2.7)	43 (3.3)	7 (2.5)
Socioeconomic status (SES)					
1 highest	5,476 (41.5)	3,857 (42.3)	976 (39.3)	536 (40.8)	107 (37.7)
2	6,120 (46.3)	4,164 (45.6)	1,221 (49.2)	599 (45.6)	136 (47.9)
3 lowest	1,611 (12.2)	1,106 (12.1)	286 (11.5)	178 (13.6)	41 (14.4)

Antidepressant use					
No	12,905 (97.7)	8,993 (98.5)	2,348 (94.6)	1,291 (98.3)	273 (96.1)
Yes	302 (2.3)	134 (1.5)	135 (5.4)	22 (1.7)	11 (3.9)
Smoking					
No	11,992 (90.8)	8,264 (90.5)	2,230 (89.8)	1,237 (94.2)	261 (91.9)
Yes	1,215 (9.2)	863 (9.5)	253 (10.2)	76 (5.8)	23 (8.1)
Physical activity					
High	7,392 (56.0)	5,354 (58.7)	1,180 (47.5)	723 (55.1)	135 (47.5)
Intermediate	2,874 (21.8)	1,900 (20.8)	621 (25.0)	277 (21.1)	76 (26.8)
Low	2,941 (22.3)	1,873 (20.5)	682 (27.5)	313 (23.8)	73 (25.7)
The Framingham Offspring type 2 diabetes risk score; mean (SD)	5.4 (5.3)	4.0 (3.8)	4.0 (3.7)	15.5 (4.2)	16.0 (4.1)

*N refers to the sum of participants (n of person-observations) in total and across the three study cycles.

Supplemental Table S1 - *Characteristics of the participants at baseline by prediabetes status and psychological distress. Figures are number (%) unless otherwise stated.*

Prediabetes status, risk level (FRS) and psychological distress at baseline	No. of person- obser- vations	No. of incident cases	Odds ratio (95% confidence interval) for incident type 2 diabetes							
			Comparison 1*	Comparison 2	Comparison 3	Comparison 4	Comparison 5	Comparison 6	Comparison 7	
All	13,207	550								
Normoglycemia – FRS 0-9 – no distress	8,025	129	1.00 (Ref.)	0.83 (0.58-1.18)	0.27 (0.19-0.36)	0.21 (0.13-0.34)	0.10 (0.08-0.13)	0.09 (0.06-0.14)	0.05 (0.03-0.06)	
Normoglycemia – FRS 0-9 – distress	2,220	41	1.20 (0.84-1.71)	1.00 (Ref.)	0.32 (0.21-0.48)	0.25 (0.14-0.44)	0.12 (0.09-0.18)	0.11 (0.07-0.19)	0.06 (0.04-0.08)	
Normoglycemia – FRS 10-18 – no distress	1,102	66	3.77 (2.76-5.14)	3.13 (2.10-4.68)	1.00 (Ref.)	0.79 (0.47-1.33)	0.39 (0.28-0.53)	0.36 (0.23-0.56)	0.18 (0.12-0.26)	
Normoglycemia – FRS 10-18 – distress	263	20	4.78 (2.92-7.83)	3.98 (2.29-6.91)	1.27 (0.75-2.15)	1.00 (Ref.)	0.49 (0.30-0.81)	0.45 (0.25-0.82)	0.23 (0.13-0.38)	
Prediabetes – FRS 10-18 – no distress	1,028	152	9.69 (7.49-12.53)	8.06 (5.62-11.54)	2.57 (1.88-3.52)	2.03 (1.23-3.33)	1.00 (Ref.)	0.92 (0.60-1.40)	0.50 (0.31-0.78)	
Prediabetes – FRS 10-18 – distress	213	33	10.55 (6.94-16.04)	8.77 (5.39-14.28)	2.80 (1.77-4.42)	2.20 (1.22-3.99)	1.09 (0.71-1.66)	1.00 (Ref.)	0.50 (0.32-0.78)	
Prediabetes – FRS >18	285	81	21.26 (15.50-29.15)	17.67 (11.82-26.43)	5.64 (3.90-8.17)	4.44 (2.62-7.54)	2.19 (1.60-3.01)	2.02 (1.28-3.18)	1.00 (Ref.)	

– no distress

Prediabetes – FRS>18	71	28	41.26 (24.82-68.59)	34.30 (19.58-60.09)	10.96 (6.39-18.79)	8.62 (4.43-16.79)	4.26 (2.55-7.10)	3.91 (2.13-7.17)	1.94 (1.13-3.34)
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– distress

Models are adjusted for age, sex, socioeconomic status, ethnicity, smoking, physical activity, and antidepressant use.

FRS: Framingham Offspring Type 2 Diabetes Risk Score.

*All comparisons are based on the same data, but they have a different reference group.

Supplemental Table S2 – *The incidence of type 2 diabetes at follow-up among participants with normoglycemia and participants with prediabetes at baseline; participants further stratified by the level of Framingham Offspring Type 2 Diabetes Risk Score (FRS) and psychological distress. Alternative reference groups are shown in comparisons 1 to 8.*