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Crump, Casey; Sundquist, Jan; Winkleby, Marilyn A; Sundquist, Kristina

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PO Box 117
221 00 Lund
+46 46-222 00 00

**STRESS RESILIENCE IN 1.5 MILLION YOUNG MEN
AND SUBSEQUENT RISK OF TYPE 2 DIABETES**

Casey Crump,¹ Jan Sundquist,² Marilyn A. Winkleby,³ Kristina Sundquist²

¹Department of Medicine, Stanford University, Stanford, California, USA

²Center for Primary Health Care Research, Lund University, Malmö, Sweden

³Stanford Prevention Research Center, Stanford University, Stanford, California, USA

Corresponding author: Casey Crump, Department of Medicine, Stanford University, 1265

Welch Road, MSOB X212, Stanford, California 94305-5411, USA. Tel: (650) 721-2400. Fax:

(650) 498-7750. Email: kccrump@stanford.edu

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ABSTRACT

Aims/hypothesis: Psychosocial stress in adulthood has been associated with higher risk of type 2 diabetes, possibly mediated by behavioral and physiologic factors. However, it is unknown whether low stress resilience earlier in life is related to subsequent development of type 2 diabetes. We examined whether low stress resilience in late adolescence is associated with increased risk of type 2 diabetes in adulthood.

Methods: National cohort study of all 1,534,425 military conscripts in Sweden during 1969-1997 (97-98% of all 18-year-old males nationwide each year) without prior diagnosis of diabetes, who underwent standardized psychological assessment for stress resilience (1-9 scale) and were followed up for type 2 diabetes identified from outpatient and inpatient diagnoses during 1987-2012 (maximum attained age 62 years).

Results: There were 34,008 men diagnosed with type 2 diabetes in 39.4 million person-years of follow-up. Low stress resilience was associated with an increased risk of developing type 2 diabetes, after adjusting for body mass index (BMI), family history of diabetes, and individual and neighborhood socioeconomic factors (hazard ratio for lowest vs. highest quintile, 1.51; 95% CI 1.46, 1.57; $P < 0.0001$), including a strong linear trend across the full range of stress resilience ($P_{\text{trend}} < 0.0001$). This association did not vary by BMI level, family history of diabetes, or socioeconomic factors.

Conclusions/interpretation: These findings suggest that low stress resilience may play an important long-term role in etiologic pathways for type 2 diabetes. Further elucidation of the underlying causal factors may help inform more effective preventive interventions across the lifespan.

Keywords: diabetes mellitus, type 2; resilience, psychological; stress, psychological

Abbreviations: BMI (body mass index), CDC (Centers for Disease Control and Prevention), CI (confidence interval), HPA (hypothalamic-pituitary-adrenal), HR (hazard ratio), ICD (International Classification of Diseases), SD (standard deviation), SES (socioeconomic status)

INTRODUCTION

Type 2 diabetes prevalence has more than doubled among US adults over the past 3 decades and now exceeds 8% [1], and may reach one-third by 2050 [2]. Obesity and physical inactivity are well-established risk factors, but less is known about psychosocial effects on disease risk. Some evidence has suggested that traumatic life events [3], job strain [4], general emotional stress [5-7], and anxiety or depression [8, 9] are associated with higher risk of developing type 2 diabetes. The underlying mechanisms may involve both behavioral and stress-related physiologic factors. Psychosocial stress may contribute to unhealthy lifestyle behaviors that are known risk factors for diabetes, such as poor dietary habits, physical inactivity, or smoking or alcohol abuse [5, 10]. Chronic stress also activates the hypothalamic-pituitary-adrenal (HPA) axis resulting in increased cortisol levels that may contribute to abdominal obesity [11, 12], and cytokine-mediated immunologic responses that may be involved in mediating insulin resistance [13]. As a result, resilience to stress may be expected to be protective against type 2 diabetes. However, to our knowledge, no studies have examined whether stress resilience early in life is related to the risk of developing type 2 diabetes in adulthood. Such knowledge may provide new insights on psychosocial pathways for diabetes and help inform more effective preventive strategies.

We conducted the first study to examine stress resilience in late adolescence in relation to type 2 diabetes risk in adulthood. Stress resilience was measured using standardized psychological assessments in ~1.5 million 18-year-old male military conscripts in Sweden during 1969-1997, who were subsequently followed up to a maximum age of 62 years. Our aim was to determine whether low stress resilience in late adolescence is associated with higher risk of developing type 2 diabetes in a large national cohort.

METHODS

Study Population

We identified 1,547,478 males (age 18 years) who underwent a military conscription examination during 1969-1997. This examination was compulsory for all 18-year-old males nationwide each year except for 2-3% who either were incarcerated or had severe chronic medical conditions or disabilities documented by a physician. We excluded all 13,053 (0.8%) individuals who had a prior diagnosis of diabetes identified from hospital discharge diagnoses. A total of 1,534,425 (99.2% of the original cohort) remained for inclusion in the study. This study was approved by the Regional Ethics Committee of Lund University in Sweden.

Stress Resilience Ascertainment

The Swedish Military Conscription Registry contains information from a 2-day standardized physical and psychological examination administered annually to all Swedish military conscripts starting in 1969. Stress resilience was assessed using a 20-30 minute semi-structured interview administered by a trained psychologist [14]. The overall objective of the interview was to assess the ability to cope with psychological requirements of military service, including stress resilience during armed combat. In the interview, the psychologist asked about adjustment problems and conflicts, as well as successes, responsibilities taken on, and initiatives shown or experienced in school, work, home, or in leisure activities [14]. Emotional stability, social maturity, and active/passive interests were rated by the psychologist, who then assigned a summary score on a “standardized nine” (1 to 9) scale, which is constructed to have a normal distribution with a mean of 5 and standard deviation (SD) of 2. A validation study in which 30

recorded interviews from 1972-1973 were scored by 30 psychologists reported high interrater reliability (correlation 0.86) [15]. Low stress resilience using these data has previously been examined in relation to other outcomes, including coronary heart disease [16], stroke [17], and peptic ulcer disease [18].

Type 2 Diabetes Ascertainment

The study cohort was followed up through December 31, 2012 for type 2 diabetes, which was identified using *International Classification of Diseases (ICD)* diagnosis codes in the Swedish Hospital Registry and Swedish Outpatient Registry. The Swedish Hospital Registry contains all primary and secondary hospital discharge diagnoses from six populous counties in southern Sweden starting in 1964, and with nationwide coverage starting in 1987; and the Swedish Outpatient Registry contains outpatient diagnoses nationwide starting in 2001. Because earlier *ICD* versions did not distinguish between type 1 and type 2 diabetes, we ascertained type 2 diabetes using *ICD-9* code 250 (excluding codes 250.X1 and 250.X3) during 1987-1996, and *ICD-10* code E11 during 1997-2012. A sensitivity analysis was performed which further included all diabetes diagnoses during 1969-1986 using *ICD-8* code 250 in hospital discharge records (before outpatient data were available), of which the majority are expected to be type 2 based on inpatient data after this period.

Adjustment Variables

Other variables that may be associated with risk of type 2 diabetes were obtained from the Swedish Military Conscription Registry and national census data, which were linked using an anonymous personal identification number. The following were used as adjustment variables:

year of the military conscription examination (modeled simultaneously as a continuous and categorical [1969-1979, 1980-1989, 1990-1997] variable); body mass index (BMI = [weight in kg]/[height in m]²; modeled alternatively as a continuous or categorical variable using Centers for Disease Control and Prevention [CDC] definitions for children and adolescents aged 2 to 19 years to facilitate comparability with US studies: overweight is defined as $\geq 85^{\text{th}}$ and $< 95^{\text{th}}$ percentile and obesity as $\geq 95^{\text{th}}$ percentile on the CDC's 2000 sex-specific BMI-for-age growth charts, which correspond to BMI ≥ 25.6 and < 29.0 and BMI ≥ 29.0 , respectively, for 18-year-old males [19]); family history of diabetes in a parent or sibling (yes or no, identified from medical diagnoses in the Swedish Hospital Registry from 1964-2012 and the Swedish Outpatient Registry from 2001-2012, not self-reported, thus enabling unbiased ascertainment); highest attained education level during the study period (< 12 , 12-14, ≥ 15 years); and neighborhood socioeconomic status (SES, included because neighborhood characteristics have been associated with type 2 diabetes [20] and with psychosocial stress [21]; comprised of an index that includes low education level, low income, unemployment, and social welfare receipt, as previously described [22], and categorized as low [> 1 SD below the mean], medium [within 1 SD from the mean], or high [> 1 SD above the mean]).

Missing data for each variable were imputed using a standard multiple imputation procedure based on the variable's relationship with all other covariates [23]. Missing data were relatively infrequent for stress resilience (7.2%), BMI (7.2%), education level (0.4%), and neighborhood SES (9.1%). Data were complete for all other variables. As an alternative to multiple imputation, sensitivity analyses were performed after restricting to individuals with complete data for all variables (N=1,327,760; 86.5%).

Statistical Analysis

Cox proportional hazards regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between stress resilience level and subsequent risk of type 2 diabetes. The Cox model time scale was elapsed time since the military conscription examination (which also corresponds to attained age because baseline age was the same [18 years] for all conscripts). Individuals were censored at emigration (n=86,400; 5.6%) or death (n=58,835; 3.8%). Stress resilience was modeled alternatively as a categorical variable (1 to 9) or an ordinal variable to test for trend. Two different adjusted models were performed: the first was adjusted for year of the military conscription examination, and the second was further adjusted for BMI, family history of diabetes, education level, and neighborhood SES (as defined above). The proportional hazards assumption was assessed by examination of log-log plots and was met in all models. Likelihood ratio tests were used to assess for first-order interactions between stress resilience and the model covariates in relation to type 2 diabetes risk. All statistical tests were 2-sided and used an α -level of 0.05. All analyses were conducted using Stata version 13.0.

RESULTS

Among the 1,534,425 men in this cohort, 34,008 (2.2%) were subsequently diagnosed with type 2 diabetes in 39.4 million person-years of follow-up (average follow-up of 25.7 years). The median age at the end of follow-up was 46.1 years (mean 45.9, SD 8.9, range 19.0 to 62.0). The median age at diagnosis of type 2 diabetes was 46.8 years (mean 44.7, SD 9.9, range 18.0 to 62.0).

Stress Resilience

Figure 1 shows the distribution of stress resilience scores (1-9 scale) in men who did or did not develop type 2 diabetes. Low stress resilience was associated with increased risk of developing type 2 diabetes (Table 1). In the fully adjusted model, men in the lowest quintile of stress resilience had a 1.5-fold risk of type 2 diabetes relative to those in the highest quintile (adjusted HR, 1.51; 95% CI 1.46, 1.57). There was a highly significant linear trend in the risk of type 2 diabetes across the full range of stress resilience ($P_{\text{trend}} < 0.0001$). Figure 2 shows the adjusted HRs and 95% CIs for type 2 diabetes across the full range of stress resilience, relative to men with average resilience as the reference group. A steep slope of increasing risk is seen for men with below-average stress resilience, whereas above-average resilience is slightly protective relative to the mean.

Other Risk Factors

High BMI was the strongest risk factor for development of type 2 diabetes. Obese men ($\geq 95^{\text{th}}$ percentile on the CDC's 2000 sex-specific BMI-for-age growth chart) had more than a 6-fold risk, and overweight men ($\geq 85^{\text{th}}$ and $< 95^{\text{th}}$ percentile) had more than a 3-fold risk, relative to those with normal BMI (Table 1, adjusted model 2). A first-degree family history of diabetes was associated with more than a 2-fold risk of developing type 2 diabetes (Table 1). High education was associated with lower risk ($P_{\text{trend}} < 0.0001$). In the fully adjusted model, neighborhood SES had a backward J-shaped relationship with type 2 diabetes risk, with highest risk corresponding to low neighborhood SES and a modestly increased risk with high neighborhood SES, relative to the intermediate group (Table 1).

There was no evidence of statistical or biologically meaningful interaction between stress resilience and BMI, family history, education level, or neighborhood SES in relation to type 2 diabetes risk. For example, among men with normal BMI, overweight, or obesity, respectively, the adjusted HRs for lowest vs. highest quintile of stress resilience were 1.51 (95% CI 1.45, 1.57; $P<0.001$), 1.50 (95% CI 1.36-1.66; $P<0.001$), and 1.52 (95% CI 1.33, 1.73; $P<0.001$) ($P_{\text{interaction}}=0.17$). Further adjustment for depression ($n=54,553$; 3.6%) and anxiety ($n=58,926$; 3.8%), ascertained from inpatient and outpatient diagnoses and modeled as time-dependent variables, also had minimal effect on the results (e.g., adjusted HR for lowest vs. highest quintile of stress resilience, 1.49; 95% CI 1.44, 1.54; $P<0.001$). In sensitivity analyses that included diabetes diagnoses from 1969-1986 (for which type 1 and type 2 could not be distinguished), or that were restricted to individuals without any missing data, all risk estimates were very similar to the main results (data not shown).

DISCUSSION

In this large national cohort study, we found that low stress resilience in 18-year-old males was associated with increased risk of developing type 2 diabetes during an average follow-up of ~25 years, independently of BMI at baseline, family history, or socioeconomic factors. These findings suggest that psychosocial function and ability to cope with stress may play an important long-term role in etiologic pathways for type 2 diabetes. Additional studies will be needed to elucidate the specific underlying causal factors, which may help inform more effective preventive interventions across the lifespan.

To our knowledge, this is the first study to examine stress resilience in late adolescence in relation to diabetes risk in adulthood. Most previous studies have focused on stressful

experiences later in adulthood in relation to diabetes. For example, a cross-sectional study of 2,262 Dutch middle-aged adults reported that major stressful life events (e.g., death of a family member) in the past 5 years was associated with higher risk of type 2 diabetes, and with increased waist-to-hip ratio [3]. A pooled cohort study of 124,808 European adults reported that job strain was associated with modestly higher risk of type 2 diabetes among both men and women [4]. Other studies have reported that general emotional stress [5], feelings of anger [6] or hostility [7], and anxiety or depression [8, 9] are risk factors for type 2 diabetes. A Swedish study of 237,980 military conscripts (a subset of the present study cohort) found that low stress resilience was associated with modestly increased risk of coronary heart disease, but did not examine diabetes or other risk factors for heart disease [16].

High BMI, which was measured at age 18, was the strongest risk factor for diabetes in this cohort. The risk estimates that we observed (more than 6-fold and 3-fold risk for obese and overweight men, respectively) are overall consistent with previously reported estimates for BMI measured in adulthood [24]. The >2-fold risk we observed among men with a family history of diabetes, and the inverse relationship between education level and diabetes risk, also were in agreement with previous findings [25, 26]. In addition, we found that low neighborhood SES was associated with higher risk of type 2 diabetes, consistent with previously reported associations between neighborhood characteristics and diabetes risk, including studies of neighborhood deprivation and walkability in Sweden [20].

The mechanisms by which stress resilience may influence the development of type 2 diabetes are likely complex and involve unhealthy lifestyle behaviors as well as other physiologic factors. A Danish cohort study of 7,066 adults with 10 years of follow-up found that self-reported perceived stress was associated with subsequent physical inactivity and

unsuccessful smoking cessation or alcohol reduction among men and women, and development of diabetes among men [5]. Anxiety and depression also are associated with physical inactivity, unhealthy diet, and smoking [10]. In addition, hormonal and immunologic factors that are involved in stress reactions may play a role in the pathogenesis of type 2 diabetes. Many forms of stress can activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in increased synthesis and release of cortisol, which contributes to lipolysis, body fat redistribution favoring visceral adiposity, and insulin resistance [11]. Chronic stress also activates the innate immune system, resulting in increased levels of interleukin-6 and other cytokine mediators of the acute-phase response, which are involved in mediating insulin resistance and are strong predictors of type 2 diabetes [13]. Additional studies with longitudinal behavioral and physiologic measurements are needed to delineate the most critical factors and windows of susceptibility across the lifespan.

Strengths of this study include its large national cohort design with prospective ascertainment of stress resilience and type 2 diabetes. This was the first study with sufficient follow-up to examine stress resilience in late adolescence in relation to diabetes in adulthood. Stress resilience was assessed using systematic interviews by trained psychologists with high interrater reliability. The national cohort design prevented selection bias, and the use of prospectively-obtained registry data prevented bias that may result from self-reporting. We were able to adjust for other established risk factors for type 2 diabetes, including BMI, family history, and socioeconomic factors, which also were prospectively ascertained and not self-reported.

Limitations included a lack of information on certain other diabetes risk factors, such as smoking and diet. The association we observed between low stress resilience and type 2 diabetes is not necessarily causal and potentially may be explained by unmeasured confounders. Because

the study was based on Swedish military conscripts, the cohort consisted entirely of men, and it is uncertain how findings would compare in women. A much smaller Danish cohort study reported that perceived stress was associated with unhealthy behaviors among both men and women, but with diabetes only among men, although the sex-specific confidence intervals were wide and overlapped [5]. The present cohort also was relatively young (median attained age 46 years). Additional follow-up to older ages will be needed whenever feasible in this or other cohorts. In addition, outpatient diagnoses in the present study were available starting in 2001, and hence type 2 diabetes prior to this period was underreported. This underreporting is expected to be nondifferential with respect to stress resilience level, and therefore to influence results toward the null hypothesis.

In summary, this large national cohort study is the first to examine stress resilience in late adolescence in relation to diabetes risk in adulthood. We found that low stress resilience is associated with higher risk of developing type 2 diabetes. Further elucidation of the underlying pathways may help improve preventive strategies by addressing important psychosocial factors across the lifespan.

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DUALITY OF INTEREST

The authors declare that there is no duality of interest associated with this manuscript.

CONTRIBUTION STATEMENT

CC, JS, MW, and KS made substantial contributions to study conception and design; analysis and interpretation of data; critical revision for important intellectual content; and approved the final version. In addition, JS and KS acquired the data, and CC drafted the manuscript.

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Table 1. Adjusted hazard ratios for associations between stress resilience or other factors in 18-year-old males and risk of type 2 diabetes in adulthood.

	Type 2 Diabetes		Adjusted Model 1 ^a			Adjusted Model 2 ^b		
	No (N=1,500,417)	Yes (N=34,008)	HR	95% CI	P	HR	95% CI	P
Stress resilience								
1 (lowest)	30,183 (2.0)	1,433 (4.2)	2.31	2.18, 2.45	<0.001	1.89	1.78, 2.00	<0.001
2	82,704 (5.5)	3,120 (9.2)	1.90	1.82, 1.98	<0.001	1.54	1.48, 1.61	<0.001
3	166,019 (11.1)	5,482 (16.1)	1.55	1.50, 1.61	<0.001	1.34	1.29, 1.39	<0.001
4	274,475 (18.3)	6,659 (19.6)	1.25	1.21, 1.30	<0.001	1.15	1.11, 1.19	<0.001
5 (reference)	383,401 (25.5)	7,278 (21.4)	1.00			1.00		
6	260,528 (17.4)	4,847 (14.3)	0.95	0.92, 0.99	0.01	0.98	0.95, 1.02	0.39
7	191,159 (12.7)	3,178 (9.3)	0.85	0.81, 0.89	<0.001	0.93	0.89, 0.97	<0.001
8	86,750 (5.8)	1,556 (4.6)	0.84	0.80, 0.89	<0.001	0.97	0.91, 1.02	0.23
9 (highest)	25,198 (1.7)	455 (1.3)	0.78	0.71, 0.86	<0.001	0.91	0.82, 1.00	0.05
Per higher category (trend)			0.86	0.85, 0.86	<0.001	0.91	0.90, 0.91	<0.001
Lowest vs. highest quintile			1.98	1.91, 2.05	<0.001	1.51	1.46, 1.57	<0.001
Body mass index								
Normal	1,388,856 (92.6)	25,918 (76.2)	1.00			1.00		
Overweight	79,952 (5.3)	4,522 (13.3)	3.78	3.66, 3.90	<0.001	3.35	3.25, 3.46	<0.001
Obese	31,609 (2.1)	3,568 (10.5)	8.42	8.12, 8.73	<0.001	6.66	6.43, 6.91	<0.001
Per 1 BMI unit (trend)			1.10	1.09, 1.10	<0.001	1.10	1.09, 1.10	<0.001
Family history of diabetes								
No	1,164,670 (77.6)	18,251 (53.7)	1.00			1.00		
Yes	335,747 (22.4)	15,757 (46.3)	2.52	2.47, 2.58	<0.001	2.20	2.15, 2.25	<0.001
Education (years)								
<12	225,154 (15.0)	8,247 (24.2)	1.14	1.11, 1.17	<0.001	1.04	1.01, 1.06	0.02
12-14	662,094 (44.1)	16,177 (47.6)	1.00			1.00		
≥15	613,169 (40.9)	9,584 (28.2)	0.59	0.57, 0.60	<0.001	0.73	0.71, 0.75	<0.001
Per higher category (trend)			0.71	0.70, 0.72	<0.001	0.84	0.82, 0.85	<0.001
Neighborhood SES								
Low	231,265 (15.4)	7,864 (23.1)	1.43	1.39, 1.47	<0.001	1.30	1.27, 1.34	<0.001
Medium	988,613 (65.9)	21,166 (62.2)	1.00			1.00		
High	280,539 (18.7)	4,978 (14.6)	0.98	0.94, 1.01	0.12	1.13	1.09, 1.16	<0.001
Per higher category (trend)			0.81	0.79, 0.82	<0.001	0.90	0.88, 0.92	<0.001

^aAdjusted for year of military conscription exam.

^bAdjusted for year of military conscription exam, BMI, family history of diabetes, education, and neighborhood SES. The reference category for all variables is indicated by an HR of 1.00.

BMI = body mass index, HR = hazard ratio, SES = socioeconomic status.

Figure legends

Figure 1. Stress resilience (1-9 scale) in 18-year-old males who did or did not develop type 2 diabetes in adulthood (black, type 2 diabetes; gray, no type 2 diabetes).

Figure 2. Adjusted hazard ratios (HRs) and 95% confidence intervals for association between stress resilience in 18-year-old males and risk of type 2 diabetes in adulthood (adjusted for year of military conscription exam, BMI, family history of diabetes, education, and neighborhood SES) (solid line, HR; dotted lines, 95% CI).

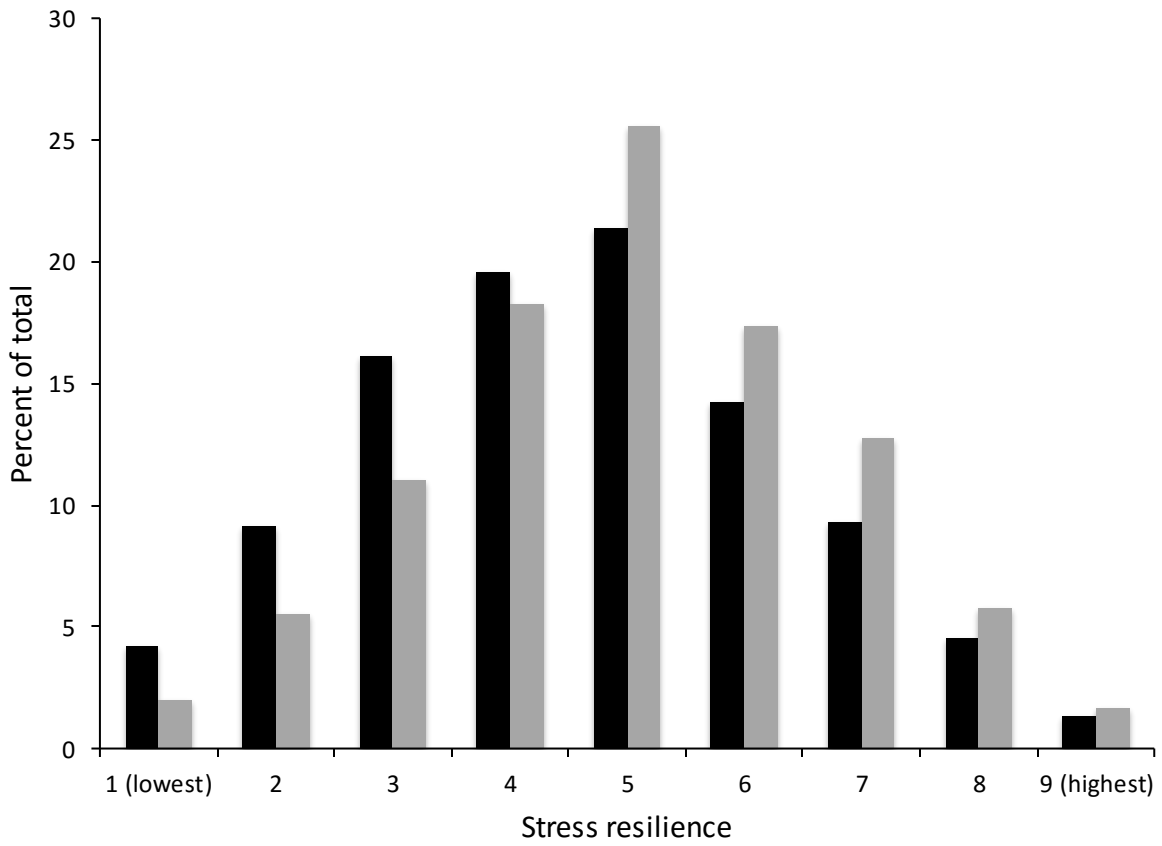


Figure 1. Stress resilience (1-9 scale) in 18-year-old males who did or did not develop type 2 diabetes in adulthood (black, type 2 diabetes; gray, no type 2 diabetes).

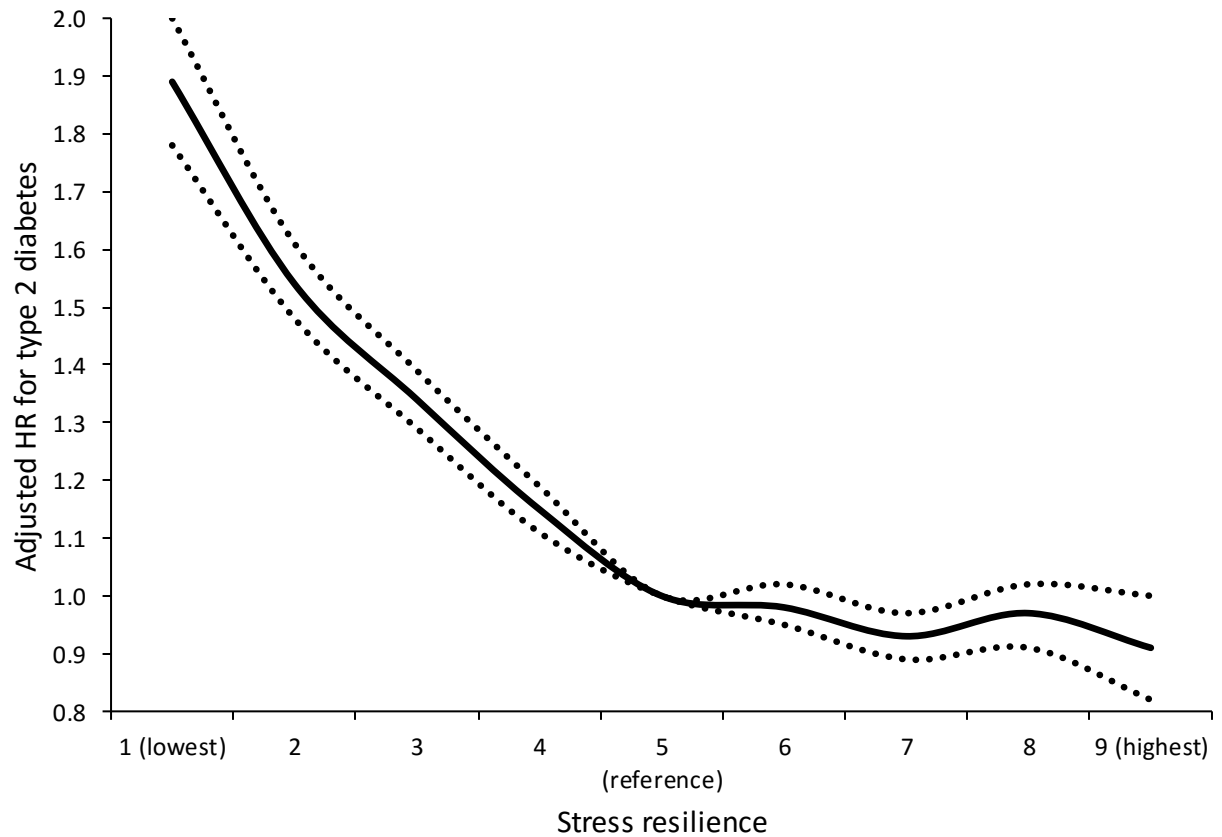


Figure 2. Adjusted hazard ratios (HRs) and 95% confidence intervals for association between stress resilience in 18-year-old males and risk of type 2 diabetes in adulthood (adjusted for year of military conscription exam, BMI, family history of diabetes, education, and neighborhood SES) (solid line, HR; dotted lines, 95% CI).