

Psychological Distress Across the Life Course and Cardiometabolic Risk



Findings From the 1958 British Birth Cohort Study

Ashley Winning, ScD, MPH,* M. Maria Glymour, ScD, MS,† Marie C. McCormick, MD, ScD,* Paola Gilsanz, ScD, MPH,* Laura D. Kubzansky, PhD, MPH*

ABSTRACT

BACKGROUND Research suggests cardiovascular and metabolic diseases are influenced by psychological distress in adulthood; however, this research is often limited to adult populations and/or a snapshot measure of distress. Given emerging recognition that cardiometabolic diseases have childhood origins, an important question is whether psychological distress earlier in life influences disease development.

OBJECTIVES This study sought to assess whether life course patterns of psychological distress assessed from childhood through adulthood predict biomarkers of cardiometabolic risk in adulthood and whether effects of sustained distress differ from more limited exposure.

METHODS The sample (n = 6,714) consists of members of the 1958 British Birth Cohort Study who completed repeated measures of psychological distress and a biomedical survey at age 45 years. Psychological distress profiles over the life course (no distress, childhood only, adulthood only, or persistent distress) were identified from 6 assessments between ages 7 and 42 years. Cardiometabolic risk was assessed by combining information on 9 biomarkers of immune, cardiovascular, and metabolic system function. Covariate adjusted linear regression models were used to assess associations between distress profiles and cardiometabolic risk.

RESULTS Compared with those with no distress, cardiometabolic risk was higher among people with psychological distress in childhood only ($\beta = 0.11$, SE = 0.03, $p = 0.0002$), in adulthood only ($\beta = 0.09$, SE = 0.03, $p = 0.007$), and persistent across the life course ($\beta = 0.26$, SE = 0.04, $p < 0.0001$).

CONCLUSIONS Psychological distress at any point in the life course is associated with higher cardiometabolic risk. This is the first study to suggest that even if distress appears to remit by adulthood, heightened risk of cardiometabolic disease remains. Findings suggest early emotional development may be a target for primordial prevention and for promoting lifelong cardiovascular health. (J Am Coll Cardiol 2015;66:1577-86) © 2015 by the American College of Cardiology Foundation.

Cardiovascular and metabolic diseases are leading causes of morbidity and mortality worldwide. Cardiovascular medicine has increasingly recognized the childhood origins of adult disease and has begun to promote strategies for primordial prevention (1). Because psychological distress is theorized to influence disease risk both

directly and indirectly, by inducing biophysical changes (2) and catalyzing health risk behaviors (3), primordial prevention strategies may benefit from considering the role of distress in cardiometabolic disease development over the life course.

The association between adult psychological distress and increased cardiometabolic risk (CMR) is

From the *Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts; and the †Department of Epidemiology and Biostatistics, University of California San Francisco School of Medicine, San Francisco, California. Dr. Winning was supported by the Julius B. Richmond Fellowship at the Harvard Center on the Developing Child, and by the Martha May Eliot Fund at the Harvard T.H. Chan School of Public Health. Dr. Gilsanz was supported by the Yerby Postdoctoral Fellowship. However, no direct funding was received or set aside for the writing of this paper. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiometabolic risk

SEP = socioeconomic position

documented by a substantial body of published reports (4); yet, little is known of the impact of psychological distress earlier in the life course (that may or may not persist through adulthood) on cardiometabolic risk.

Childhood psychological distress is commonly characterized as internalizing (e.g., depression, anxiety) and externalizing (e.g., inattention, impulsivity) symptoms. Given that most prospective cohorts with psychological measures obtained early in life are still too young to present with clinical disease endpoints, researchers have looked to biomarkers as indicators of subclinical disease (5,6). Components of cardiometabolic dysregulation (e.g., hypertension, dyslipidemia) tend to cluster, and combining information from a range of biomarkers of CMR appears to improve prediction of who is at risk of developing manifest disease (7).

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The strongest evidence linking distress to CMR is from studies of depression and inflammatory markers (8); however, much of this work is cross-sectional. One prospective study found that poor emotional functioning assessed at age 7 years was associated with higher C-reactive protein at age 42 years (9). It remains unclear whether cardiometabolic alterations may result from childhood-limited exposure alone or whether they are due to more chronic exposure with distress across the life course. The goal of the present study was to assess whether life course patterns of psychological distress assessed at childhood and into adulthood predict biomarkers of CMR in adulthood, using longitudinal data from the 1958 British Birth Cohort Study. We specifically evaluated whether effects of distress on CMR remained evident when distress appeared to be remitted by adulthood and whether effects of sustained distress differed from more limited exposure. Given that childhood social and health conditions may be a previous common cause of both distress and elevated CMR, we adjusted for relevant childhood covariates (e.g., socioeconomic position, physical health status).

METHODS

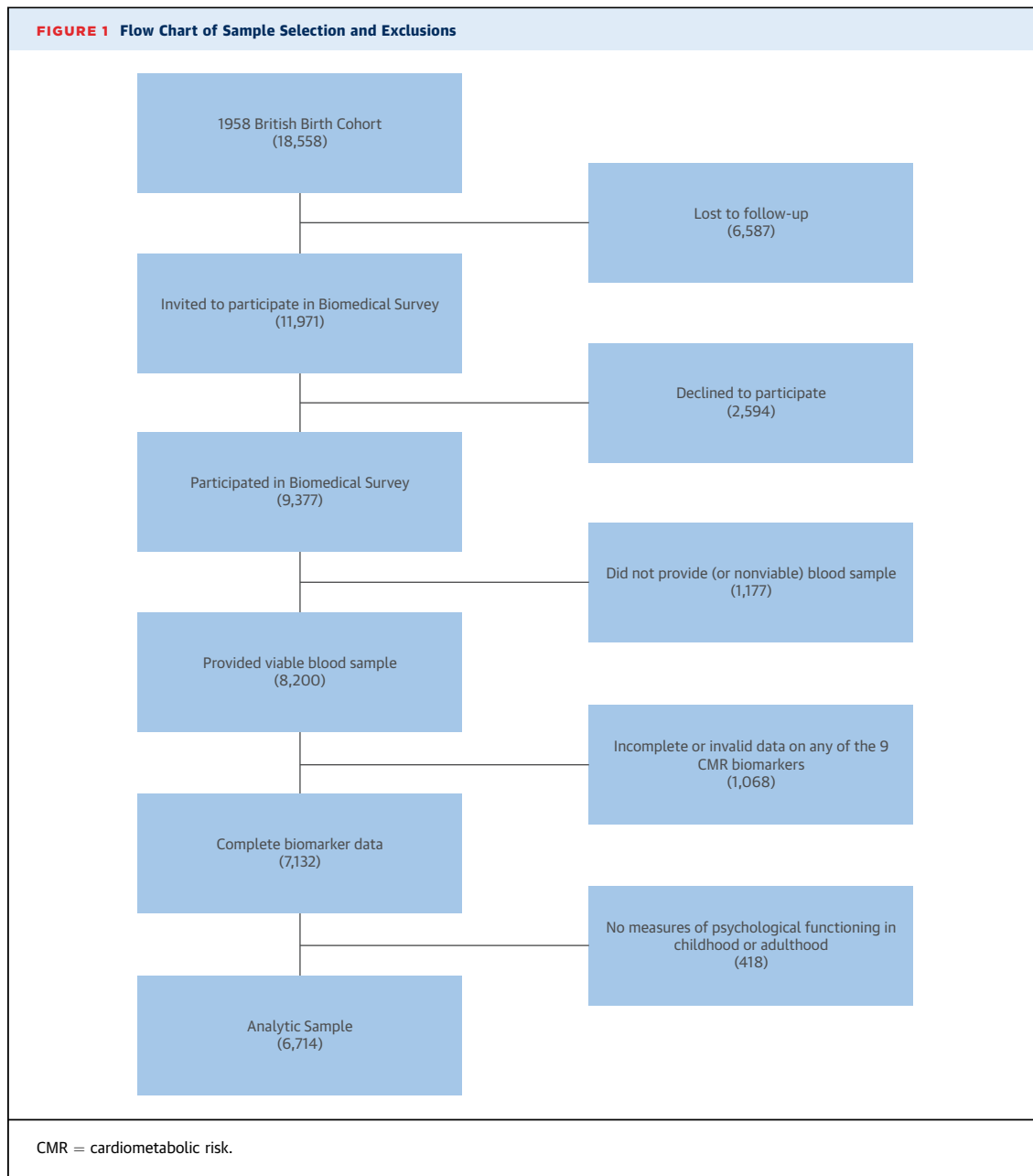
SAMPLE POPULATION. Data come from the 1958 British Birth Cohort Study—an ongoing longitudinal study of people born in Great Britain during a single week in March 1958 (N = 18,558). Detailed information was collected at birth and during 6 follow-up waves at ages 7, 11, 16, 23, 33, and 42 years. At age 45 years, 9,377 cohort members participated in a biomedical assessment. Compared with the surviving

cohort at 45 years, people with high internalizing or externalizing symptoms and low math or reading scores at age 7 were less likely to participate in the biomedical assessment (10). The 1958 British Birth Cohort Study and biomedical survey are described in detail elsewhere (11,12).

The eligible sample comprised the 8,200 participants who provided a viable blood sample and blood pressure measure at the biomedical assessment. We excluded participants who had missing or invalid data on any of the 9 biomarkers of interest (n = 1,068) and those who had no measures of distress in either childhood or adulthood (n = 418), leaving an analytic sample of 6,714 cohort members. (Figure 1 is a flow chart of sample selection and exclusions.) Compared with those excluded from the full biomedical sample, those in the analytic sample were similar, yet had slightly higher cognitive ability and lower weight in childhood and slightly higher socioeconomic position (SEP) and physical activity frequency in adulthood.

MEASURES. Childhood psychological distress was ascertained from internalizing and externalizing symptoms assessed at ages 7, 11, and 16 years. At ages 7 and 11 years, psychological distress was assessed using the validated teacher-rated Bristol Social Adjustment Guide (13). The 146-item Bristol Social Adjustment Guide measures a number of “syndromes,” representing externalizing and internalizing symptom clusters. Following previous work in this cohort (14), we assessed internalizing symptoms by combining items included in 3 relevant syndromes: depression; withdrawal; and unforthcomingness (referring to timidity). We assessed externalizing symptoms by combining items capturing 6 relevant syndromes: restlessness; inconsequential behavior (referring to attentional issues and misbehavior); hostility toward children; hostility toward adults; anxiety about acceptance by children; and anxiety about acceptance by adults (the latter 2 referring to inappropriate interpersonal self-regulation). Items included on each of the syndrome subscales were coded as “yes” = 1 or “no” = 0, and these were summed to yield a continuous internalizing (range 0 to 30) and externalizing (range 0 to 45) score at both time points. In the available sample at each wave, Cronbach alphas assessing internal consistency reliability were 0.64 at age 7 and 0.63 at age 11 years for internalizing subscales, and 0.75 at age 7 and 0.74 at age 11 years for externalizing subscales.

At age 16 years, psychological distress was assessed using the teacher version of the Rutter Behaviour Scale (15), a 26-item questionnaire designed to measure externalizing and internalizing symptoms.



Consistent with previous studies using the Rutter Behaviour Scale (14), we derived an internalizing score from summing 5 items (worried, solitary, miserable, fearful, and fussy) and an externalizing score from summing 9 items (destructive, fights, not liked, irritable, disobedient, lies, steals, bullies, and resentful/aggressive). Each item was coded as “does not apply” = 0, “somewhat applies” = 1, or “certainly applies” = 2. Higher scores indicated more severe symptoms. Cronbach alphas for these internalizing and externalizing subscales in the age 16 years sample

were 0.68 and 0.89, respectively. If participants were missing at least one-half of the internalizing or externalizing items on either measure, we set their corresponding score to missing; otherwise, for approximately 1% of the sample, we substituted missing values (typically only 1 scale item) with the mean of their completed items.

At each age in childhood (7, 11, and 16 years), we created binary internalizing and externalizing variables (high/low). Scores in the top 13% were defined as “high,” which is consistent with other work

(13,14,16). We then created a binary variable to indicate “high” distress, which categorized whether an individual had a high internalizing or externalizing score at any point during childhood. Recognizing that this method of categorizing individuals may result in loss of information, we also created a continuous summary measure of child psychological distress by standardizing the internalizing and externalizing scores and taking the mean of the standardized scores across the 3 childhood time points. Higher scores indicated greater distress. We then z-standardized this summary score, for ease of interpretation.

Adult psychological distress was measured at ages 23, 33, and 42 years using the self-report psychological distress subscale of the Malaise Inventory (17). The inventory includes 15 psychological distress items (e.g., “do you often feel miserable or depressed?”) with yes/no response options. We dealt with missing items in the same manner as in childhood. Reliability of the scale in this population was high, with Cronbach alphas ranging from 0.75 to 0.79 at each time point. Following previous work (16), if participants endorsed 5 or more of the 15 items, we classified them as having “high” distress. We then created a binary measure indicating the presence of high distress at any point in adulthood, as well as a continuous standardized summary measure of distress across the 3 adulthood time points.

PSYCHOLOGICAL DISTRESS PROFILES. Guided by the work of Power et al. (16), we created 4 mutually exclusive psychological distress profile groups. We classified participants as having “no distress” at any time point, “persistent” distress (in both childhood and adulthood), “childhood only” distress (distress at any point in childhood but never in adulthood), or “adulthood only” distress (vice versa). We also created a continuous lifespan psychological distress summary score, by taking the mean of the standardized internalizing, externalizing, and psychological distress scores across all childhood and adulthood time points. For ease of interpretation, we then standardized this summary score.

CARDIOMETABOLIC RISK. We created a CMR score on the basis of 9 biomarkers identified as relevant to cardiometabolic health (6,7), and available in the 1958 British Birth Cohort Study dataset: C-reactive protein (excluding values ≥ 10 mg/l, which may indicate acute infection) (18); fibrinogen; high-density-lipoprotein cholesterol (reverse scored); total cholesterol; triglycerides; glycosylated hemoglobin; resting heart rate; and systolic and diastolic blood pressure (both averaged across 3 measurements). Biomarkers were

assessed using standard laboratory and clinical procedures, described in detail in the biomedical survey user’s guide (19). For each biomarker, we created a standardized z-score and then summed the 9 biomarker scores to create a total CMR score, with higher scores indicating greater cardiometabolic dysregulation. We standardized the CMR summary score so that regression estimates could be interpreted in units of the population SD of CMR. For sensitivity analyses, we created an alternative “high risk” cardiometabolic score, where we tallied the number of biomarkers that met clinically defined criteria for “high risk,” thereby creating a score that ranged from 0 to 9 (20). The frequency of “high risk” levels for the biomarkers ranged from approximately 3% (for HbA1c) to 36% (for total cholesterol).

COVARIATES. Child covariates consisted of sex (male, female); SEP (on the basis of father’s occupation at child’s birth and classified according to the British Registrar General’s scale: 1) professional and managerial; 2) unskilled nonmanual; 3) skilled manual; 4) semi- or unskilled manual, or no male head of household) (21); low birth weight (< 5.5 pounds vs. ≥ 5.5 pounds); cognition at age 7 years (assessed using a 10-problem arithmetic test (22) and the Southgate Reading Test (23), with the lowest 10% of scores in each test counting as low ability) (10); overweight at age 7 years (body mass index ≥ 17.92 kg/m² for boys and ≥ 17.75 kg/m² for girls (24) as assessed by medical examiner); and presence of any physical health problems by age 7 years (any parent-reported asthma, chronic illness, or signs of heart problems; yes/no).

Adult covariates, all self-reported at age 42 years, included participants’ attained SEP; smoking status (never, past, or current); physical activity (rare, low, medium, or high); healthy diet (continuous measure on the basis of frequency of consumption of fruits, salads/raw vegetables, chips, fried food, sweets/chocolates, and biscuit/cakes) (25); and use of cardiovascular or endocrine medication (yes/no). The biomedical sample was 98% white, so race was not considered in the analyses.

STATISTICAL ANALYSIS. Linear regression models were used to assess the relationship between psychological distress profiles (no distress, childhood only, adulthood only, or persistent distress) and CMR scores, with the “no distress” category serving as the reference group. In model 1, we adjusted for sex, and in model 2, we adjusted for all child covariates. In addition to all child covariates, model 3 adjusted for

TABLE 1 Demographic Characteristics and Child Covariates, by Psychological Distress Profile

	Overall	Psychological Distress				Chi-Square p Value
		Never	Childhood Only	Adulthood Only	Persistent	
Sample size	6,714 (100.00)	3,309 (49.29)	1,683 (25.07)	1,005 (14.97)	717 (10.68)	
Sex						
Female	3,341 (49.76)	1,636 (49.44)	600 (35.65)	682 (67.86)	423 (59.00)	<0.0001
Male	3,373 (50.24)	1,673 (50.56)	1,083 (64.35)	323 (32.14)	294 (41.00)	
SEP						
Prof/manager	1,233 (18.85)	754 (23.55)	226 (13.66)	177 (18.10)	76 (10.76)	<0.0001
Nonmanual	653 (9.98)	344 (10.74)	167 (10.10)	98 (10.02)	44 (6.23)	
Manual	3,197 (48.88)	1,497 (46.75)	835 (50.48)	495 (50.61)	370 (52.41)	
Semi-/unskilled	1,457 (22.28)	607 (18.96)	426 (25.76)	208 (21.27)	216 (30.59)	
Low birth weight						
No	6,054 (95.32)	2,978 (95.85)	1,541 (95.65)	895 (94.11)	640 (93.84)	0.036
Yes	297 (4.68)	129 (4.15)	70 (4.35)	56 (5.89)	42 (6.16)	
Math score						
Normal	5,728 (95.10)	2,871 (98.32)	1,448 (92.35)	848 (95.71)	561 (86.44)	<0.0001
Low	295 (4.90)	49 (1.68)	120 (7.65)	38 (4.29)	88 (13.56)	
Reading score						
Normal	5,646 (93.29)	2,863 (97.65)	1,365 (86.89)	866 (96.76)	552 (84.40)	<0.0001
Low	406 (6.71)	69 (2.35)	206 (13.11)	29 (3.24)	102 (15.60)	
Overweight						
No	4,996 (90.61)	2,464 (91.16)	1,277 (90.95)	745 (88.27)	510 (90.59)	0.091
Yes	518 (9.39)	239 (8.84)	127 (9.05)	99 (11.73)	53 (9.41)	
Physical health problems						
No	5,554 (93.41)	2,717 (93.72)	1,415 (93.21)	823 (91.75)	599 (94.78)	0.08
Yes	392 (6.59)	182 (6.28)	103 (6.79)	74 (8.25)	33 (5.22)	

Values are n (%) and are presented before using multiple imputation techniques to impute missing covariate values. Therefore, counts for the covariates will not equal the sample total in cases where values were missing. Chi-square compares differences in covariates by psychological distress profiles.
Prof = professional; SEP = socioeconomic position.

medication use and potential pathway variables (adult SEP, smoking, physical activity, and diet).

We also ran regression models using continuous summary measures of child, adult, and lifespan psychological distress, to test the hypothesis that greater distress at each time period was associated with greater CMR in a monotonic fashion. Child, adult, and lifespan distress were entered into each model separately, with variable sets as previously specified. In a final set of models, child and adult distress were entered simultaneously. There was no significant effect of the interaction between child and adult psychological distress on the CMR score, so we do not report on this further.

For sensitivity analysis, each biomarker was tested as an individual outcome, to determine which, if any, components of the CMR score were particularly sensitive to the psychological distress profiles. We also examined the impact of distress profiles on our alternative “high risk” measure of CMR. Finally, all primary analyses were repeated with those participants who completed psychological measures at all 6 waves (n = 3,434).

Multiple imputation, using the Markov Chain Monte Carlo method (26), was used to impute missing covariate values. The proportion of missing covariates ranged from 0% for sex to 18% for body weight at age 7 years, with most covariates missing <5% of observations. Results were similar with and without imputations. The greatest source of missing data was due to participant attrition. Thus, to minimize potential bias, we conducted inverse probability weighted analyses by weighting key factors associated with attrition: male sex; lower SEP at birth; lower cognition (math and reading scores) at age 7 years; and higher internalizing and externalizing symptoms at age 7 years (10).

All analyses were performed using SAS software (version 9.3, SAS Institute, Inc., Cary, North Carolina). Access to the data, including a special license agreement for use of biomedical data, was granted by the Economic and Social Data service council, the U.K. Data Archive, and the Center for Longitudinal Studies. Ethical approval of this study was given by the Harvard T.H. Chan School of Public Health Institutional Review Board.

TABLE 2 Linear Regression of the Association Between Psychological Distress Profiles and Adult CMR (n = 6,714)

	Model 1		Model 2		Model 3	
	β (SE)	p Value	β (SE)	p Value	β (SE)	p Value
Psychological distress						
Never	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Childhood only	0.17 (0.03)	<0.0001	0.11 (0.03)	0.0002	0.06 (0.03)	0.04
Adulthood only	0.12 (0.03)	0.0006	0.09 (0.03)	0.007	0.02 (0.03)	0.64
Persistent	0.35 (0.04)	<0.0001	0.26 (0.04)	<0.0001	0.15 (0.04)	0.0001
Child covariates						
Male	0.62 (0.02)	<0.0001	0.62 (0.02)	<0.0001	0.64 (0.03)	<0.0001
Family SEP						
Prof/manager	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Nonmanual			0.12 (0.05)	0.01	0.09 (0.05)	0.07
Manual			0.25 (0.03)	<0.0001	0.19 (0.03)	<0.0001
Semi-/unskilled			0.33 (0.04)	<0.0001	0.23 (0.04)	<0.0001
Low birth weight			0.05 (0.05)	0.34	0.04 (0.05)	0.46
Low math score			0.01 (0.07)	0.89	-0.02 (0.06)	0.67
Low reading score			0.21 (0.05)	<0.0001	0.18 (0.05)	0.0002
Overweight			0.16 (0.05)	0.001	0.14 (0.04)	0.002
Physical health problems			-0.04 (0.06)	0.53	0.01 (0.05)	0.83
Adult covariates						
Cardiovascular medication					0.53 (0.04)	<0.0001
Endocrine medication					0.38 (0.04)	<0.0001
SEP						
Prof/manager					Ref.	Ref.
Nonmanual					0.03 (0.03)	0.39
Manual					0.04 (0.03)	0.23
Semi-/unskilled					0.11 (0.04)	0.002
Smoking						
Never					Ref.	Ref.
Past					0.03 (0.03)	0.26
Current					0.30 (0.03)	<0.0001
Physical activity						
High					Ref.	Ref.
Medium					0.09 (0.03)	0.007
Low					0.00 (0.03)	0.89
Rare					0.20 (0.03)	<0.0001
Healthy diet					0.00 (0.003)	0.48

Model 1 adjusts for sex; model 2 adjusts for sex and child covariates (SEP, LBW, low math score, low reading score, overweight, and physical health problems); and model 3 adjusts for sex, child covariates, and adult covariates (medication use, SEP, smoking, physical activity, and healthy diet).
CMR = cardiometabolic risk; LBW = low birth weight; Ref. = reference; other abbreviations as in Table 1.

RESULTS

SAMPLE CHARACTERISTICS. The sample had an approximately equal proportion of male and female subjects (Table 1). At birth, most respondents had a father with an occupation classified as skilled manual (48.9%), and <5% of respondents were of low birth weight. By age 7 years, 6.6% of respondents had experienced physical health problems, and at age 7 years, 4.9% had low math scores, 6.7% had low reading scores, and 9.4% were overweight. All covariates were significantly associated with the psychological distress profiles.

PSYCHOLOGICAL DISTRESS AND CARDIOMETABOLIC RISK.

Almost one-half (49.3%) of the sample reported no significant psychological distress at any point in childhood or adulthood, and 10.7% had persistent distress (both childhood and adulthood). One-quarter of the sample (25.1%) had distress only in childhood, and 15.0% had distress only in adulthood. A larger proportion of female (13%) than male participants (9%) had persistent distress.

Compared with the reference group (no distress), people with childhood only ($\beta = 0.17$, SE = 0.03, $p < 0.0001$), adulthood only ($\beta = 0.12$, SE = 0.03, $p = 0.0006$), and persistent distress ($\beta = 0.35$,

SE = 0.04, $p < 0.0001$) had significantly higher CMR scores, in sex-adjusted models (Table 2). Adjusting for the other childhood covariates in addition to sex somewhat attenuated these estimates, but all associations remained significant (Central Illustration). On average, people with persistent distress had a one-quarter SD worse CMR score than those with no distress ($\beta = 0.26$, SE = 0.04, $p < 0.0001$). This estimated effect on CMR is greater than that of being overweight in childhood ($\beta = 0.16$) and comparable to that of having lower childhood SEP (i.e., father's occupation outside of the professional and managerial classes; $\beta = 0.12$ to 0.33).

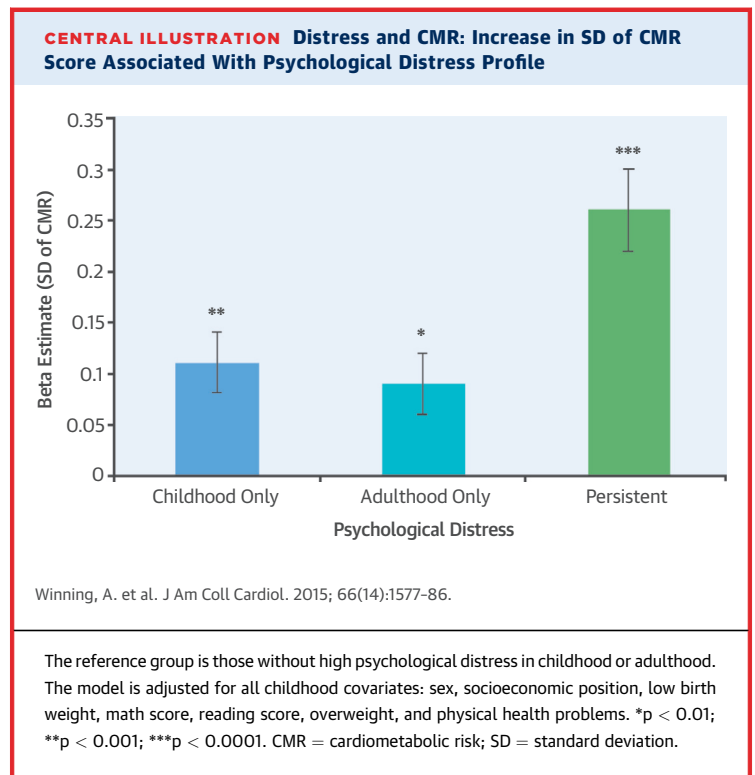
Further adjustment for medication use, adult SEP, and health behaviors in addition to all child covariates attenuated estimates such that the CMR of those with distress only in adulthood was no longer significantly different than that of those without any distress across the life course ($\beta = 0.02$, SE = 0.03, $p = 0.64$). However, relative to those with no psychological distress, individuals with distress only in childhood ($\beta = 0.06$, SE = 0.03, $p = 0.04$) and persistent distress ($\beta = 0.15$, SE = 0.04, $p = 0.0001$) still had significantly higher CMR scores in fully adjusted models.

Child, adult, and lifespan distress summary scores were each significantly and positively associated with higher CMR scores, adjusting for sex, child, and adult covariates (Table 3). When we simultaneously adjusted for both child and adult distress scores, child distress remained significantly associated with CMR in the fully adjusted model ($\beta = 0.07$, SE = 0.02, $p = 0.0001$), but the effect of adult distress attenuated to marginal significance ($\beta = 0.02$, SE = 0.01, $p = 0.09$).

Sensitivity analyses. The same trends, though generally weaker, were evident when considering each biomarker as a separate outcome; however, psychological distress was not associated with blood pressure (Table 4). Using the "high risk" cardiometabolic score instead of the CMR z-score yielded similar results, though only those with persistent distress had significantly greater "high risk" cardiometabolic scores in the fully adjusted model (Online Table 1). Results were unchanged when main analyses were restricted to those with psychological measures in all 6 waves (not shown).

DISCUSSION

This study supports growing evidence that psychological distress contributes to excess risk of cardiovascular and metabolic disease and that effects may be initiated relatively early in life. Participants in the



1958 British Birth Cohort Study who had psychological distress at any period in their lifetime were at increased risk for cardiometabolic diseases at age 45 years, as indicated by higher CMR scores. Whereas the highest CMR scores were evident among those with distress in both childhood and adulthood, this is the first study to suggest that increased risk of cardiometabolic disease associated with distress in childhood may be maintained even if distress remits by adulthood.

Considering severity, greater psychological distress in childhood was associated with higher CMR in adulthood, even when controlling for adult distress. Notably, because adult psychological distress is affected by child distress, analyses simultaneously adjusting for both child and adult distress scores likely underestimate the effects of child distress on CMR.

A wealth of published data supports a relationship between psychological distress and cardiometabolic diseases (4), and a growing number of published reports suggests that high levels of distress may lead to biological dysregulation well before frank disease manifests (8). However, such findings have been viewed cautiously on the grounds that most studies have not been able to account for the plausible alternative explanation that childhood factors (such as low SEP or obesity)

TABLE 3 Linear Regression of the Association Between Psychological Distress Summary Scores and CMR (n = 6,714)

	Model 1		Model 2		Model 3	
	β (SE)	p Value	β (SE)	p Value	β (SE)	p Value
Child score	0.20 (0.02)	<0.0001	0.14 (0.02)	<0.0001	0.08 (0.02)	<0.0001
Adult score	0.11 (0.01)	<0.0001	0.08 (0.01)	<0.0001	0.03 (0.01)	0.03
Lifespan score	0.26 (0.02)	<0.0001	0.19 (0.02)	<0.0001	0.09 (0.02)	<0.0001

Child score is the standardized average psychological distress score across waves 1 to 3 (ages 7 to 16 years). Adult score is the standardized average psychological distress score across waves 4 to 6 (ages 23 to 42 years). Lifespan score is standardized average psychological distress score across waves 1 to 6 (ages 7 to 42 years). Higher scores indicate more distress. Child, adult, and lifetime scores were entered into the models separately (i.e., they are not simultaneously adjusting for each other). Model 1 adjusts for sex; model 2 adjusts for sex and child covariates (SEP, LBW, low math score, low reading score, overweight, and physical health problems); and model 3 adjusts for sex, child covariates, and adult covariates (medication use, SEP, smoking, physical activity, and healthy diet).
Abbreviations as in Tables 1 and 2.

might contribute to both psychological distress and cardiometabolic functioning. Furthermore, most studies in this area are limited to adult populations and/or have a single measure of psychological functioning. Whereas research is increasingly exploring the impact of aspects of child psychological status on later health, few studies have looked at psychological distress comprehensively over time in relation to CMR.

Consistent with recent findings by Copeland et al. (27) that a cumulative dose of multiple depressive episodes has a more robust effect on C-reactive protein than any single depressive episode, we found that persistent psychological distress over the life course was associated with greater CMR than distress occurring in childhood or adulthood alone. Whereas effects of distress in childhood on higher CMR in adulthood appeared to be somewhat mitigated if distress levels were lower by adulthood, they were

not eradicated. This highlights the potentially lasting impact of childhood distress on adult physical health and brings up questions of “reversibility”—the notion that if distress remits, accrued biological harm can be reversed or “undone.”

The period from in utero through the early years of childhood represents a sensitive period of marked immune system plasticity, during which exposures can establish long-term patterns of immune response (28). Thus, dysregulation that emerges early in life may become more difficult to mitigate in adolescence or adulthood. This may be true for other relevant biological systems, though little work to date has addressed this systematically. McEwen (29) suggests that the successive alterations in biological stress-regulatory systems brought on by prolonged or recurrent psychological distress may be irreversible, which may explain why the apparent remission of distress by adulthood did not eliminate heightened CMR in our study.

MECHANISMS. There are a number of plausible indirect and direct mechanisms by which psychological distress could increase risk of cardiometabolic disease, comprising 2 primary pathways: behavioral and biological. For instance, distress may influence disease risk indirectly by motivating harmful behaviors such as cigarette smoking and physical inactivity (30), and/or by reducing educational and occupational achievement (31). Given there are sensitive periods for establishing behavior patterns (e.g., smoking is typically initiated in adolescence), childhood and adolescent distress may be especially influential. Psychological distress may also have a more direct biological impact on health by altering neuroendocrinological mechanisms involved in mediating the stress response, such as the hypothalamic-pituitary-adrenal axis and sympathetic adrenal medullary system (32). Chronic activation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, triggered by repeated or sustained exposure to stressful experiences, can lead to a cascade of deleterious effects on processes related to cardiometabolic functioning, including immune functioning, blood pressure, and lipid metabolism (33). Other work has suggested that high levels of distress may induce autonomic imbalance and reduced parasympathetic tone, which in turn are associated with increased risk of a range of pathological conditions including cardiovascular disease and premature mortality (34). Relevant epigenetic changes leading to glucocorticoid resistance and overexpression of angiotensinogen have also been identified (35). In the current study, both indirect

TABLE 4 Association Between Psychological Distress Profile and Individual Biomarkers, Adjusting for Sex and Child Covariates (n = 6,714)

	Psychological Distress						
	Never	Childhood Only		Adulthood Only		Persistent	
		β (SE)	p Value	β (SE)	p Value	β (SE)	p Value
Blood pressure							
Systolic	Ref.	0.02 (0.03)	0.45	-0.07 (0.04)	0.06	-0.02 (0.04)	0.67
Diastolic	Ref.	0.03 (0.03)	0.41	0.008 (0.04)	0.83	0.007 (0.04)	0.87
Cholesterol							
HDL	Ref.	0.04 (0.03)	0.16	0.14 (0.04)	0.0001	0.28 (0.04)	<0.0001
Total	Ref.	0.04 (0.03)	0.15	0.007 (0.04)	0.83	0.07 (0.04)	0.09
CRP	Ref.	0.05 (0.03)	0.11	0.04 (0.04)	0.27	0.19 (0.04)	<0.0001
Fibrinogen	Ref.	0.07 (0.03)	0.03	0.07 (0.04)	0.07	0.20 (0.04)	<0.0001
HbA _{1c}	Ref.	0.09 (0.03)	0.002	0.03 (0.04)	0.39	0.14 (0.04)	0.0006
Heart rate	Ref.	0.12 (0.03)	0.0002	0.09 (0.04)	0.01	0.15 (0.04)	0.0003
Triglycerides	Ref.	0.06 (0.03)	0.05	0.14 (0.04)	0.0002	0.25 (0.04)	<0.0001

CRP = C-reactive protein; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; Ref. = reference.

and direct mechanisms appear to be relevant. Adjustment for adult SEP and health behaviors attenuated associations, suggesting that these covariates may partially mediate the relationship between distress and CMR. However, that the effect was not fully explained by these factors suggests other mediators are possible.

STUDY LIMITATIONS AND STRENGTHS. The measures of psychological distress and assessment of remission were not comprehensive. For example, we did not have measures in adulthood equivalent to externalizing symptoms in childhood, and we rely on teacher reports of childhood distress, which tend to document fewer symptoms (especially internalizing symptoms) than do child self-reports (36). It is also possible that those in the “no distress” group experienced some distress outside of the assessment time points; however, if this were the case, it would likely mean that our findings underestimate the true effect of distress on CMR. Furthermore, given that we could only assess presence or absence of distress symptoms, we are unable to comment on potential cardiometabolic health improvement associated with enhanced psychological well-being. Given the observational nature of the data and the absence of biomarkers before mid-adulthood, we cannot completely rule out the possibility of unmeasured confounding or reverse causation. Furthermore, we were unable to adjust for use of psychotropic medications, which have implications for CMR. Finally, the study is limited by participant attrition; however, we conducted weighted analyses to minimize potential bias associated with attrition. This study has many additional strengths, including a large unselected sample, follow-up spanning 45 years, prospective (repeated) measures of psychological distress (which protect against the risk of recall bias), and multiple

data collection sources/methods (which protect against potential method bias).

CONCLUSIONS

Should current findings be replicated, an important next step will be to evaluate systematically whether reducing psychological distress in childhood indeed improves subsequent CMR, as well as which types of intervention are most effective and at what ages. It would be additionally informative to explore the impact of early adversity on these relationships. Whereas the causes of cardiometabolic diseases are multifactorial, childhood psychological factors tend to be understudied. Our findings point to childhood distress as relevant for both screening and intervention related to adult cardiometabolic disease prevention, and they provide support for the importance of attending to early emotional development as a primordial prevention strategy.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Ashley Winning, Department of Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, 677 Huntington Avenue, Kresge 7th Floor, Boston, Massachusetts 02115. E-mail: awinning@mail.harvard.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: Current symptoms of psychological distress and symptoms of distress across the lifespan should be considered during cardiovascular risk assessment.

TRANSLATIONAL OUTLOOK: Randomized trials should be developed to assess whether preventing or improving childhood distress influences biomarkers of CMR later in life.

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APPENDIX For a supplemental table, please see the online version of this article.