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Associations between anxious-depressed symptoms and cardiovascular risk factors in a longitudinal childhood study

Sandra Louise
University of Western Australia, slouise@meddent.uwa.edu.au

Nicole Warrington
University of Western Australia, nicole.warrington@uwa.edu.au

Pamela McCuskie
University of Western Australia, pamela.mccuskie@qmail.com

Wendy Oddy
University of Western Australia, wendyo@ichr.uwa.edu.au

Stephen Zubrick
University of Western Australia, steve@ichr.uwa.edu.au

See next page for additional authors

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Authors
Sandra Louise, Nicole Warrington, Pamela McCuskie, Wendy Oddy, Stephen Zubrick, Beth P. Hands, Trevor Mori, Laurent Briollais, Sven Silburn, Lyle Palmer, Eugene Mattes, and Lawrence Beilin

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Sandra Louise [a,*], Nicole M. Warrington [b], Pamela A. McCaskie [a], Wendy H. Oddy [c], Stephen R. Zubrick [c], Beth Hands [d], Trevor A. Mori [e], Laurent Briollais [f], Sven Silburn [c,g], Lyle J. Palmer [a,f,h], Eugen Mattes [c], Lawrence J. Beilin [e]

[a] Centre for Genetic Epidemiology and Biostatistics, the University of Western Australia, Perth, Australia
[b] School of Women's and Infants' Health, The University of Western Australia, Perth, Australia
[c] Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Australia
[d] University of Notre Dame, Fremantle, Australia
[e] School of Medicine and Pharmacology, Royal Perth Hospital Unit, The University of Western Australia, Perth, Australia
[f] Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Canada
[g] Developmental Health and Education Research, Menzies School of Health Research, Darwin, Australia
[h] Dalla Lana School of Public Health, University of Toronto and Cancer Care Ontario, Toronto, Canada

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ABSTRACT

Objective. To examine the influence of anxious/depressed scores on cardiovascular risk factors throughout childhood.

Methods. Data from the Western Australian Pregnancy Cohort (Raine) Study, a study of 2900 pregnancies recruited between 1989 and 1991, were used. Anxious-depressed scores (derived from the Childhood Behavior Checklist), body mass index (BMI) and blood pressure were measured at 5 (n = 1681), 8 (n = 1697), 10 (n = 1575) and 14 (n = 1386) years. At age 14 depressive symptom scores (Beck Depression Inventory for Youth), anxious-depressed scores (Youth Self-Report (YSR) and Teacher Report Form (TRF)) and fasting lipid, glucose and insulin were also available. Cross sectional and longitudinal analyses were conducted.

Results. At age 14, girls with higher anxious-depressed scores had higher BMI ($p \leq 0.005$) and homeostasis model assessment-estimated insulin resistance ($p \leq 0.0001$). This equated to a difference of 0.6 kg/m^2 and 0.3 units in predicted BMI and HOMA-IR respectively (top 5% vs. score of zero). Boys with higher anxious-depressed scores had lower systolic blood pressure trajectories ($p = 0.024$).

Conclusion. Depressive scores appear to have differing influences on BMI, homeostasis model assessment-estimated insulin resistance and systolic blood pressure in boys and girls. Paradoxically boys with higher anxious-depressed scores had lower blood pressure throughout childhood.

Introduction

Depressive symptoms have been consistently and independently associated with cardiovascular disease (CVD) risk and mortality (Hemingway and Marmot, 1999; Nicholson et al., 2006; Rugulies, 2002; Wulsin and Singal, 2003). CVD risk factors (Adams et al., 2005; Chen and Wang, 2008; Klumbiene et al., 2000; Porkka et al., 1994; Webber et al., 1991; Zimmet et al., 1992) and depressive symptoms (Costello et al., 2006; Pine et al., 1998) both show origins in childhood and track from adolescence to adulthood. Given the complex and multidirectional nature of the relationship between depression and CVD in adults, examining the influences of depressive symptoms on CVD risk factors in childhood may shed some light on the nature of this association.

Consistent with adult studies, children with more depressive symptoms are at increased risk of being obese (Cortese et al., 2009; Goodman and Whitaker, 2002; Hillman et al., 2010; Mustillo et al., 2003; Richardson et al., 2006). Few childhood studies, however, have examined the influence of depressive symptoms on CVD risk factors other than obesity. One cross-sectional study reported an inverse association between negative affect and blood pressure in boys (Ewart and Kolodner, 1994) and another reported an association between depressive symptoms and insulin sensitivity (Shomaker et al., 2010). Therefore in addition to BMI, the aim of this study was to

Abbreviations: BMI, Body mass index; YSR, Youth Self-Report; TRF, Teacher Report Form; HOMA-IR, Homeostasis model of assessment; CVD, Cardiovascular disease; KEMH, King Edward Memorial Hospital; BDI-Y, Beck Depression Inventory for Youth; CBCL, Child Behavior Checklist; LME, Linear mixed effect.

* Corresponding author at: M409, University of Western Australia, 35 Stirling Hwy Crawley, Western Australia 6009, Australia.
E-mail address: slouise@meddent.uwa.edu.au (S. Louise).

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investigate the cross sectional and longitudinal childhood associations between depression scores and a range of cardiovascular and related metabolic risk factors.

Participants and methods

Study population

This study uses data from participants of the Western Australian Pregnancy Cohort (Raine) Study, a longitudinal pregnancy cohort of children whose mothers attended antenatal clinic at King Edward Memorial Hospital (KEMH) or nearby private practices in Western Australia between 1989 and 1991. More specific details of recruitment have been published elsewhere (Newnham et al., 1993). The original cohort consisted of 2900 pregnant women, recruited at approximately 18 weeks of gestation. Depression related measures and certain CVD risk factors were assessed at 5, 8, 10 and 14 years.

At each survey self reported questionnaires were completed by the child's primary carer (usually their mother (~85%)) and also by the child at age 14. At 10 and 14 years the child's school teacher also completed a questionnaire relating to the child's performance and behavior at school. Anthropometry and blood pressure measurements were obtained at each assessment visit, and at age 14 blood samples were taken for fasting lipids, glucose and insulin.

Participants were excluded from this study if they were part of a multiple pregnancy, had a major congenital malformation, or had a related sibling in the study. Parents of participants gave informed consent at each survey as did the children at age 14. The study was approved by Human Ethics Committees at King Edward Memorial Hospital and Princess Margaret Hospital in Perth.

Anxious/depressed mood

Anxious-depressed scores were available from the Child Behavior Checklist (CBCL/4-18) at all surveys (Achenbach, 1991a), from the Youth Self Report (YSR/11-18) at 14 years and from the Teacher Report Forms (TRF/6-18) at 10 and 14 years (Achenbach, 1991b).

The anxious-depressed subscales within both the CBCL/4-18 and YSR/11-18 consisted of 13 items relating to anxious and/or depressive mood including whether the child cries a lot, is nervous, too fearful or anxious. Scores could range from zero to 26. The TRF/6-18 subscale consisted of 16 items and scores could range from zero to 32. Higher scores represented greater anxious-depressed mood (Achenbach, 1991a).

Depressive symptoms were measured using the Beck Depression Inventory for Youth (BDI-Y) in the 14 year survey (Beck et al., 2001). The BDI-Y contains 20 items relating solely to depressed symptoms that an adolescent may have felt in the last 2 weeks. Scores could range from zero to 60.

Both measures have excellent test–retest reliability (BDI-Y: girls: $r = 0.87$; boys: $r = 0.89$) (Beck et al., 2001) and high sensitivity (CBCL/4-18: 66% anxious-depressed) and specificity (CBCL/4-18: 80% anxious-depressed) (Zubrick et al., 1997). Consistent with previous studies (Costello et al., 2006; Sawyer et al., 2001), at each survey less than 5% of the cohort were anxious-depressed as defined by Achenbach (1991a). Therefore our focus was on how changes in anxious-depressed scores over time affected the rate of change (longitudinal) or mean measures (cross sectional) of CVD risk factors within the cohort (Pine et al., 1997). For consistency we analysed the BDI-Y similarly (8.4% were mildly, moderately or severely depressed according to the clinical thresholds defined by Beck et al. (2001)).

CVD risk factors

Weight, height and blood pressure were assessed by trained assessors (Huang et al., 2007, 2009). Weight was recorded to the nearest 100 g using a Wedderburn digital chair scale; height, to the nearest 0.1 cm, was measured using a Holtain Stadiometer. Body mass index (BMI) was then calculated. Seated blood pressure was measured after a 5 minute rest using a Dinamap electronic recorder (Dinamap XL or Dinamap ProCare 100), with the appropriate sized cuff placed on the right arm. With the exception of blood pressure measured at year 8 when only two readings were obtained, the second and third readings recorded at 2 minute intervals were averaged for each child (Schulze et al., 2000).

Fasting triglycerides, high-density lipoprotein cholesterol (HDL-C) total cholesterol, insulin and glucose were measured in most children attending ($n = 1297$) at 14 years (Huang et al., 2009). Triglycerides and total cholesterol were determined enzymatically on a Cobas MIRA analyzer (Roche Diagnostics) and HDL-C was determined on a heparin–manganese supernatant (Huang et al., 2009). Glucose and insulin were measured by an automated Technicon Axon analyzer (Bayer Diagnostics, Australia) and an automated radioimmunoassay (Tosoh, Japan) respectively. HOMA-IR and low density lipoprotein cholesterol (LDL-C) were then calculated using the formula fasting insulin (μU/mL) × fasting glucose (mmol/L) / 22.5 (Matthews et al., 1985) and the Friedewald formula (Friedewald et al., 1972) respectively.

Statistical analysis

Three sets of analyses were conducted.

1. Cross sectional analyses between anxious/depressed scores and BMI and blood pressure at 5, 8, 10 and 14 years.
2. Cross sectional analyses between anxious/depressed scores and fasting lipids and HOMA-IR at 14 years.
3. Longitudinal analyses between anxious-depressed scores over time on BMI and blood pressure trajectories.

Cross-sectional analyses

For skewed data $\log_e$ transformations were applied prior to analysis; for diastolic blood pressure in boys at 8 years and girls at 5 years, systolic blood pressure at 14 years in boys, triglycerides and HOMA-IR in both boys and girls at age 14, HDL-C, LDL-C and total cholesterol in girls at age 14. Multivariate skew-normal linear regression (Azzalini and Capitanio, 1999) was used to account for the longer right trail of BMI distribution, present at all surveys even after $\log_e$ transformation.

If an association was detected, multivariate linear regression analyses were performed with adjustment for the following potential confounders: age, age^2, age of first menstruation as an indicator of puberty (available for females only), socio economic status (Goodman, 1999) as indicated by family income measured at 5, 8, 10 and 14 years, BMI (where appropriate), diet (assessed 14 years only using the food frequency questionnaire (Oddy et al., 2009), the higher the score the better the diet), smoking in the last 12 months, vigorous exercise frequency and duration outside of school.

Longitudinal analyses

Trajectories were constructed to examine the influence of longitudinal measures of anxious-depressive scores (derived from the CBCL/4-18) on the CVD risk factors of BMI, systolic and diastolic blood pressure.

Diastolic and systolic blood pressure trajectories were constructed using linear mixed effect (LME) models (Laird and Ware, 1982) from 5 to 14 years. Due to the non-normality of BMI measurements across time, an extension of the LME model based on multivariate skew t distribution (Lachos et al., 2010) was used to construct BMI trajectories. As we are interested in changes in BMI overtime, we have opted to look at untransformed BMI measures as other transformation methods such as z scores have been shown to be optimal for assessing adiposity at a single occasion (Cole et al., 2005).

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All trajectories included random effects for intercept (average systolic blood pressure, diastolic blood pressure or BMI) and slope (change in systolic blood pressure, diastolic blood pressure or BMI over time). If a longitudinal association was detected, adjustments were made for potential confounders (low income and BMI (blood pressure trajectories only)).

All analyses were stratified by sex due to significant sex and anxious-depressed score interactions for most CVD risk factors ($p<0.05$). All continuous confounders were mean centered (to the nearest whole number) to remove potential co-linearity between the beta coefficients. Analyses were performed in the statistical package R version 2.6.1 (R Development Core Team, 2007). Only significant confounders were left in the final adjusted model. As this study was exploratory in nature, multiple testing was corrected for by dividing the initial significance level (5%) by the number of different endpoints tested (blood pressure, BMI, fasting lipids and HOMA-IR (i.e. n = 4)) (Bender and Lange, 2001).

Results

Of the original 2900 pregnancies, 2633 were eligible for analysis after excluding multiple pregnancies (n = 66), fetus or babies that did not survive birth (n = 91), newborns with congenital malformations (n = 29), babies with later complications (n = 2) and/or related siblings (n = 79). The number of children at the 5, 8, 10 and 14 year surveys with complete data was 1681, 1697, 1575 and 1386 respectively. The proportion of males and females remained consistent (~52% female) and 82% of parents reported that they were Caucasian.

Characteristics of children with complete data at 5 to 14 years are shown in Table 1. At 14 years boys exercised more and for longer, had better diet quality, higher systolic blood pressure, lower BMI, lower fasting lipid measurements and lower anxious-depressed and depressive symptom scores compared to girls. By age 14, 89.0% of girls had their menstrual period.

Children who participated at 14 years compared to those lost to follow-up after 5 years of age had higher systolic blood pressure (103.6 mm Hg vs. 102.3 mm Hg, $p = 0.010$) and were from higher income families (≥$40 001 = 46.9% vs. 38.9%, $p = 0.002$); all other measures were comparable.

Cross sectional analyses

Boys at 14 years with higher depressive symptom scores had lower systolic blood pressure ($p = 0.002$). Boys for whom teachers reported more anxious-depressed symptoms had higher triglyceride measurements ($p = 0.008$) (Table 2). Only the association between systolic blood pressure and depressive symptoms was independent of potential confounders (Table 3). Using adjusted models the predicted mean difference between systolic blood pressure of boys with a depressive symptom score (BDI-Y ≥ 15) in the top 5% and those who had no symptoms was −3.0 mm Hg.

Table 1
Characteristics of participants of the Western Australian Pregnancy Cohort (Raine) Study at all surveys of interest with complete data (1989 to 2006).

Survey	Boys				Girls			
	5	8	10	14	5	8	10	14
N	865	876	825	706	816	821	750	680
Age (years)	5.9 (0.01)	8.1 (0.01)	10.6 (0.01)	14.1 (0.01)	5.9 (0.01)	8.1 (0.01)	10.6 (0.01)	14.1 (0.01)
Systolic blood pressure (mm Hg)	103.2 (0.3)	103.7 (0.3)	106.8 (0.3)	**113.8 (0.4)**	103.1 (0.3)	103.8 (0.4)	106.3 (0.4)	**108.9 (0.4)**
Diastolic blood pressure (mm Hg)	54.4 (0.3)	56.0 (0.2)	56.6 (0.2)	58.3 (0.3)	55.0 (0.3)	56.5 (0.2)	56.7 (0.2)	59.2 (0.3)
BMI (kg/m^2)[a]	15.6 (14.8, 16.5)	16.2 (15.2, 17.5)	17.7 (16.4, 20.0)	**19.9 (18.3, 22.7)**	15.5 (14.7, 16.6)	16.3 (15.2, 18.0)	18.0 (16.4, 20.5)	**20.7 (18.9, 23.3)**
Family income[b]								
$1–$25,000	258 (29.8)	191 (21.8)	173 (21.0)	93 (13.2)	236 (28.9)	160 (19.5)	156 (20.8)	84 (12.4)
$25,001–$40,000	223 (25.8)	193 (22.0)	129 (15.6)	101 (14.3)	215 (26.4)	212 (25.8)	152 (20.3)	128 (18.8)
≥$40,001	384 (44.4)	492 (56.2)	523 (63.4)	512 (72.5)	365 (44.7)	449 (54.7)	442 (58.9)	468 (68.8)
Race[b]								
Caucasian	744 (86.0)	741 (84.6)	709 (85.9)	615 (87.1)	685 (84)	688 (83.8)	638 (85.1)	575 (84.6)
Asian	35 (4.0)	40 (4.6)	33 (4.0)	26 (3.7)	30 (3.7)	25 (3.0)	26 (3.5)	23 (3.4)
Other	86 (9.9)	95 (10.8)	83 (10.1)	65 (9.2)	101 (12.4)	108 (13.2)	86 (11.5)	82 (12.1)
Anxious-depressed (CBCL/4-18)[a]	2.0 (1,4)	2.0 (1,5)	2.0 (0,4)	**1.0 (0,3)**	2.0 (1,4)	2.0 (1,5)	2.0 (0,4)	**2.0 (0,4)**
Anxious-depressed (YSR/11-18)[a]	–	–	–	**2.0 (1,5)**	–	–	–	**4.0 (2,7)**
Depressive symptoms (BDI-Y)[a]	–	–	–	**3.0 (1,8)**	–	–	–	**6.0 (2,12)**
Puberty–age at first period	–	–	–	–	–	–	–	12.8 (0.05)
Ever smoked[b]								
Yes	–	–	–	51 (7.3)	–	–	–	63 (9.3)
No	–	–	–	651 (92.7)	–	–	–	613 (90.7)
Diet quality	–	–	–	**81.5 (0.6)**	–	–	–	**79.1 (0.6)**
Exercise frequency outside of school hours[b]								
≥4 times a week	–	–	–	**284 (40.3)**	–	–	–	**172 (25.3)**
1–3 times a week	–	–	–	**373 (53.0)**	–	–	–	**430 (63.2)**
Once a month or less	–	–	–	**47 (6.7)**	–	–	–	**78 (11.5)**
Exercise duration outside of school hours[b]								
≥7 h a week	–	–	–	**115 (16.3)**	–	–	–	**46 (6.8)**
2–6 h a week	–	–	–	**382 (54.2)**	–	–	–	**353 (51.9)**
Less than 1 h a week	–	–	–	**208 (29.5)**	–	–	–	**281 (41.3)**
Measures available on subset								
N	**–**	**–**	770	417	**–**	**–**	701	420
Anxious-depressed mood score (TRF/6-18)[a]	–	–	**1.0 (0,3)**	0.0 (0,1)	–	–	**1.0 (0,2)**	0.0 (0,2)
N	–	–	–	581	–	–	–	543
HOMA-IR	–	–	–	2.6 (0.1)	–	–	–	2.6 (0.1)
Triglycerides (mmol/L)	–	–	–	1.0 (0.2)	–	–	–	1.0 (0.02)
LDL-C (mmol/L)	–	–	–	**2.3 (0.03)**	–	–	–	**2.4 (0.03)**
HDL (mmol/L)	–	–	–	**1.3 (0.01)**	–	–	–	**1.4 (0.01)**
Total cholesterol (mmol/L)	–	–	–	**4.1 (0.03)**	–	–	–	**4.3 (0.03)**

Values represent means and standard errors of the mean unless indicated by [a](representing medians (interquartile range) for skewed data) or [b](representing n (%) for categorical data). '–' represents measures that were not assessed. Values in bold represent significant difference between males and females.

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Table 2
Cross sectional associations between anxious/depressed scores and systolic blood pressure (SBP) and body mass index (BMI) in the Western Australian Pregnancy Cohort (Raine) Study at years 5, 8, 10 and 14 (from 1989 to 2006) and triglycerides and HOMA-IR at year 14.

CVD risk factors	CBCL	Males				Females			
		n	β	95% CI	*p* value	n	β	95% CI	*p* value
SBP (mm Hg)	P5	865	0.087	(−0.105, 0.280)	0.373	816	−0.139	(−0.350, 0.071)	0.195
	P8	876	−0.070	(−0.254, 0.113)	0.453	821	0.056	(−0.150, 0.261)	0.595
	P10	825	−0.079	(−0.281, 0.124)	0.445	750	−0.008	(−0.221, 0.205)	0.941
	TRF10	770	−0.085	(−0.302, 0.132)	0.444	701	0.065	(−0.200, 0.330)	0.630
	P14	706	−0.177	(−0.435, 0.082)	0.173	680	0.145	(−0.046, 0.337)	0.137
	YSR	706	−0.258	(−0.483, −032)	0.023	680	−0.024	(−0.175, 0.127)	0.755
	TRF14	417	−0.277	(−0.719, −0.167)	0.213	420	0.292	(−0.038, 0.622)	0.083
	BDI	**706**	**−0.237**	**(−0.385, −0.088)**	**0.002**	680	−0.029	(−0.121, 0.062)	0.529
BMI (kg/m^2)	P5	865	0.002	(−0.026, 0.031)	0.874	816	−0.008	(−0.039, 0.024)	0.634
	P8	876	−0.009	(−0.038, 0.021)	0.563	821	0.012	(−0.022, 0.045)	0.491
	P10	825	0.018	(−0.022, 0.059)	0.379	750	0.042	(−0.005, 0.090)	0.082
	TRF10	770	−0.022	(−0.068, 0.023)	0.341	701	0.007	(−0.065, 0.079)	0.844
	P14	706	−0.025	(−0.094, 0.044)	0.479	680	0.073	(0.013, 0.132)	0.016
	YSR	706	−0.019	(−0.080, 0.043)	0.555	**680**	**0.075**	**(0.029, 0.121)**	**0.001**
	TRF14	417	0.016	(−0.105, 0.136)	0.800	**420**	**0.160**	**(0.065, 0.255)**	**0.001**
	BDI	706	−0.033	(−0.074, 0.008)	0.110	**680**	**0.041**	**(0.012, 0.069)**	**0.005**
Triglycerides (mmol/L)	P14	581	0.002	(−0.010, 0.013)	0.780	543	0.008	(−0.002, 0.017)	0.098
	YSR	581	0.005	(−0.005, 0.015)	0.279	543	0.006	(−0.001, 0.013)	0.086
	TRF14	**364**	**0.023**	**(0.006, 0.0404)**	**0.008**	356	0.005	(−0.011, 0.0211)	0.527
	BDI	581	0.004	(−0.003, 0.010)	0.236	543	0.003	(−0.001, 0.008)	0.134
HOMA.IR	P14	581	−0.003	(−0.045, 0.039)	0.881	543	0.032	(0.005, 0.059)	0.018
	YSR	581	−0.007	(−0.043, −0.030)	0.714	**543**	**0.036**	**(0.017, 0.056)**	**0.0002**
	TRF14	364	0.056	(−0.006, 0.119)	0.073	356	0.050	(0.008, 0.093)	0.017
	BDI	581	−0.018	(−0.042, −0.006)	0.135	**543**	**0.024**	**(0.012, 0.036)**	**<0.0001**

PX scores derived from the Child Behavior Checklist (CBCL/4-18), YSR scores derived from the Youth Self Report CBCL, TRFX derived from Teacher Reported Form and BDI-Y scores are derived from the Beck Depression Inventory for Youth.
Values in bold represent associations that survived correction for multiple testing ($p \leq 0.013$).
β values above represent the amount of change in each specified CVD risk factor for a one-unit change in anxious/depressed score.

At 14 years girls with higher anxious-depressed and depressive symptom scores tended to have higher HOMA-IR and BMI (Table 2). Only the association between scores reported by child's teacher and BMI were independent of potential confounders (Table 3). Using adjusted models the predicted mean difference between the BMI and HOMA-IR of girls with an anxious-depressed score in the top 5% (TRF/6-18 ≥ 6 and YSR/11-18 ≥ 15 respectively) and those who had no symptoms were respectively 0.6 kg/m^2 and 0.3 units. No other associations were found ($p > 0.013$) (see online Supplement Table A.1).

Longitudinal analyses

Boys with higher anxious-depressed scores over time had a lower rate of change for systolic blood pressure (Fig. 1). This persisted after adjusting for BMI (β = −0.037; 95% CI: −0.070, −0.005; $p = 0.024$). No other longitudinal associations were detected (see online Supplemental Table A.2).

Discussion

In this study anxious-depressed symptoms influenced cardiovascular risk factors differently in boys and girls. At 14 years, girls with higher anxious-depressed scores had higher adiposity and insulin resistance, possibly predicting the coincidental development of adult depression and cardiovascular disease. On the other hand boys with higher anxious depressed scores had lower systolic blood pressure trajectories throughout childhood.

Two other studies have also reported associations between depressive symptoms and adiposity only in girls (Chaiton et al., 2009; Hillman et al., 2010). A possible mechanism underlying the gender differences between anxious-depressive scores and adiposity at age 14 may be sex-related differences in hormones such as leptin. Leptin is a key regulator of body weight (Kaplowitz et al., 2001), is thought to trigger puberty (Blum et al., 1997), has been linked to depressed mood (Lu, 2007) and has been shown to be present at greater concentrations in young women compared to age-matched men (Castracane et al., 1998).

Shomaker et al. (2010) reported that depressive symptoms in adolescence were related to decreased insulin sensitivity, independent of adiposity, puberty and sex. In our study, however, this relationship was apparent only in girls. In contrast to the study used by Shomaker et al. (2010), our sample was larger, younger and had a lower proportion of obese children. Both studies were correlational in nature and as such the direction of causality remains unclear.

Our finding of an inverse association between anxious/depressed scores and systolic blood pressure in adolescent boys but not girls is consistent with a previous study (Ewart and Kolodner, 1994). Our longitudinal analyses suggest that this association is present as early as 5 years of age. At first sight the direction of this association appears contrary to studies in which adults with more depressive symptoms were at increased risk of hypertension (Davidson et al., 2000; Delaney et al., 2010). However a study by Licht et al. (2009) showed that adults who were depressed, excluding those taking anti depressant, had lower blood pressure while depression defined by antidepressant use increased the risk of hypertension. Alternatively this relationship may depend on adult behaviors and responses to environmental stress (Lett et al., 2004). It is also possible that the continuous measures of anxious-depressed mood used in this study have lower predictive value (Lustman and Clouse, 2007) for subsequent clinically diagnosed depression in adults which have been associated with cardiovascular events.

Elovainio et al. (2010) showed from 3 years of age, children with steeper triglyceride trajectories were more likely to have more depressive symptoms as adults. In our study adolescent boys with higher anxious-depressed scores (teacher reported) had higher fasting triglycerides levels. This association appeared dependent on BMI and exercise. Anxious-depressed scores in our study were reliant on the perception of a child's primary carer, the child and/or the child's school teacher. Thus the different associations in this study may reflect differing relationships between the reporter and child and the environment in which the observations take place (Achenbach et al., 1987).

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Table 3
Multivariate associations between anxious/depressed scores and cardiovascular risk factors in the Western Australian Pregnancy Cohort (Raine) Study that survived multiple testing (2003 to 2006).

Sex	Outcome	Predictor[a]	Effect size	95% CI	*p* value
Boys	Systolic blood pressure (mm Hg) (n = 705)	Family income >$25,001 and <$40,000	2.826	(−0.027, 5.751)	0.048
		≥$40,001	1.830	(−0.406, 4.109)	0.103
		BMI	0.766	(0.583, 0.948)	<0.0001
		BDI-Y	**−0.200**	**(−0.339, −0.060)**	**0.004**
	Triglycerides (mmol/L) (n = 363)	Age	0.241	(0.023, 0.514)	0.026
		BMI	0.026	(0.017, 0.035)	<0.0001
		Exercise frequency outside of school hours			
		1–3 times a week	0.072	(−0.031, 0.189)	0.169
		once a month or less	0.120	(−0.001, 0.258)	0.048
		TRF14	0.013	(−0.002, 0.028)	0.078
Girls	HOMA.IR (n = 508)	Year of first period	0.020	(0.008, 0.033)	0.001
		BMI	0.017	(0.014, 0.021)	<0.0001
		Exercise frequency outside of school hours			
		1–3 times a week	0.061	(0.028, 0.096)	0.0001
		Once a month or less	0.070	(0.020, 0.126)	0.004
		BDI-Y	**0.002**	**(0.001, 0.004)**	**0.007**
	HOMA.IR (n = 508)	Year of first period	0.124	(0.052, 0.198)	0.0005
		BMI	0.104	(0.084, 0.124)	<0.0001
		Exercise frequency outside of school hours			
		1–3 times a week	0.373	(0.175, 0.587)	0.0001
		Once a month or less	0.439	(0.141, 0.777)	0.002
		YSR	**0.020**	**(0.004, 0.037)**	**0.014**
	BMI (kg/m^2) (n = 638)	Year of first period	−0.754	(−0.944, −0.564)	0.0001
		Family income >$25,001 and <$40,000	−0.519	(−1.322, 0.284)	0.206
		≥$40,001	−0.714	(−1.382, −0.047)	0.036
		YSR	0.030	(−0.015, 0.075)	0.191
	BMI (kg/m^2) (n = 638)	Year of first period	−0.772	(−0.962, −0.583)	0.0001
		Family income >$25,001 and <$40,000	−0.505	(−1.315, 0.305)	0.222
		≥$40,001	−0.704	(−1.375, −0.034)	0.039
		BDI-Y	0.007	(−0.020, 0.034)	0.599
	BMI (kg/m^2) (n = 396)	Year of first period	−0.763	(−0.974, −0.551)	0.0001
		Family income >$25,001 and <$40,000	−0.415	(−1.387, 0.558)	0.403
		≥$40,001	−0.886	(−1.691, −0.081)	0.031
		TRF14	**0.105**	**(0.015, 0.195)**	**0.023**

YSR scores derived from the Youth Self Report CBCL, TRFX derived from Teacher Reported Form and BDI-Y scores are derived from the Beck Depression Inventory for Youth.
Values in bold represent significant associations.
Effect size values above represent the amount of change in each specified outcome for a one-unit change in each listed predictor.
[a] Only significant predictors left in final model. ≤$25,000 = baseline category of family income; ≥4 times a week = baseline category for exercise frequency.

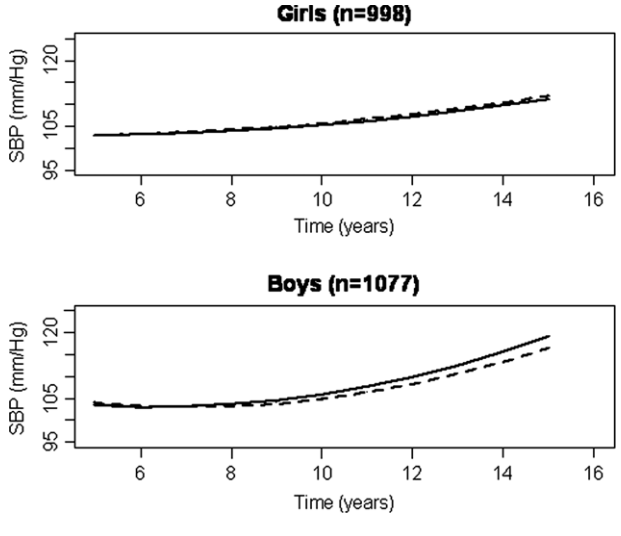

Fig. 1. Predicted systolic blood pressure (SBP) trajectories in boys and girls in the Western Australian Pregnancy Cohort (Raine) Study for those whose primary carer reported no anxious-depressed symptoms compared to those who met Achenbach's classification of anxious-depressed throughout childhood (CBCL ≥ 10 and 11 respectively) (1989 to 2006).

Study limitations and strengths

Limitations of our study include attrition and the correlational nature of this study. Children who continued to participate in this study, however, were comparable to those who were lost to follow-up except in relation to family income and systolic blood pressure. A strength of our study was the use of detailed quantitative trait measurements that were measured consistently and collected serially. Unlike many previous studies, we were able to explore longitudinal associations and therefore explore the potential aetiological pathways underlying the association of anxious-depressed mood and CVD risk factors overtime.

In summary, anxious/depressed symptoms were associated with higher BMI and insulin resistance in girls and lower systolic blood pressure throughout childhood in boys. These effects are present prior to the development of unhealthy lifestyles that may contribute to the association between CVD and depression in adulthood.

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Conflict of interest statement

There were no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.ypmed.2012.03.004.

References

Achenbach, T.M., 1991a. Manual for the Child Behavior Checklist/4-18 and 1991 Profile. University of Vermont, Department of Psychiatry, Burlington.
Achenbach, T.M., 1991b. Manual for the Youth Self-Report and 1991 Profile. University of Vermont, Department of Psychiatry, Burlington.
Achenbach, T.M., Mcconaughy, S.H., Howell, C.T., 1987. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. Psychol. Bull. 101, 213–232.
Adams, C., Burke, V., Beilin, L.J., 2005. Cholesterol tracking from childhood to adult mid-life in children from the Busselton study. Acta Paediatr. 94, 275–280.
Azzalini, A., Capitanio, A., 1999. Statistical applications of the multivariate skew-normal distribution. J. R. Stat. Soc. B Methodol. 61, 579–602.
Beck, J.S., Beck, A.T., Jolly, J.B., 2001. Beck Youth Inventories of Emotional and Social Impairment. The Psychological Corporation, United States of America.
Bender, R., Lange, S., 2001. Adjusting for multiple testing—when and how? J. Clin. Epidemiol. 54, 343–349.
Blum, W.F., Englaro, P., Hanitsch, S., Juul, A., Hertel, N.T., Muller, J., Skakkebaek, N.E., Heiman, M.L., Birkett, M., et al., 1997. Plasma leptin levels in healthy children and adolescents: dependence on body mass index, body fat mass, gender, pubertal stage, and testosterone. J. Clin. Endocrinol. Metab. 82, 2904–2910.
Castracane, V.D., Kraemer, R.R., Franken, M.A., Kraemer, G.R., Gimpel, T., 1998. Serum leptin concentration in women: effect of age, obesity, and estrogen administration. Fertil. Steril. 70, 472–477.
Chaiton, M., Sabiston, C., O'loughlin, J., Mcgrath, J.J., Maximova, K., Lambert, M., 2009. A structural equation model relating adiposity, psychosocial indicators of body image and depressive symptoms among adolescents. Int. J. Obes. (Lond.) 33, 588–596.
Chen, X., Wang, Y., 2008. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 117, 3171–3180.
Cole, T.J., Faith, M.S., Pietrobelli, A., Heo, M., 2005. What is the best measure of adiposity change in growing children: BMI, BMI %, BMI z-score or BMI centile? Eur. J. Clin. Nutr. 59, 419–425.
Cortese, S., Falissard, B., Angriman, M., Pigaiani, Y., Banzato, C., Bogoni, G., Pellegrino, M., Cook, S., Pajno-Ferrara, F., et al., 2009. The relationship between body size and depression symptoms in adolescents. J. Pediatr. 154, 86–90.
Costello, E.J., Erkanli, A., Angold, A., 2006. Is there an epidemic of child or adolescent depression? J. Child Psychol. Psychiatry 47, 1263–1271.
Davidson, K., Jonas, B.S., Dixon, K.E., Markovitz, J.H., 2000. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. Arch. Intern. Med. 160, 1495–1500.
Delaney, J.A., Oddson, B.E., Kramer, H., Shea, S., Psaty, B.M., Mcclelland, R.L., 2010. Baseline depressive symptoms are not associated with clinically important levels of incident hypertension during two years of follow-up: the multi-ethnic study of atherosclerosis. Hypertension 55, 408–414.
Elovainio, M., Pulkki-Raback, L., Kivimaki, M., Jokela, M., Viikari, J., Raitakari, O.T., Telama, R., Keltikangas-Jarvinen, L., 2010. Lipid trajectories as predictors of depressive symptoms: the Young Finns study. Health Psychol. 29, 237–245.
Ewart, C.K., Kolodner, K.B., 1994. Negative affect, gender, and expressive style predict elevated ambulatory blood pressure in adolescents. J. Pers. Soc. Psychol. 66, 596–605.
Friedewald, W.T., Levy, R.I., Fredrickson, D.S., 1972. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin. Chem. 18, 499–502.
Goodman, E., 1999. The role of socioeconomic status gradients in explaining differences in US adolescents' health. Am. J. Public Health 89, 1522–1528.
Goodman, E., Whitaker, R.C., 2002. A prospective study of the role of depression in the development and persistence of adolescent obesity. Pediatrics 110, 497–504.
Hemingway, H., Marmot, M., 1999. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ 318, 1460–1467.
Hillman, J.B., Dorn, L.D., Bin, H., 2010. Association of anxiety and depressive symptoms and adiposity among adolescent females, using dual energy X-ray absorptiometry. Clin. Pediatr. (Phila.) 49, 671–677.
Huang, R.C., Burke, V., Newnham, J.P., Stanley, F.J., Kendall, G.E., Landau, L.I., Oddy, W.H., Blake, K.V., Palmer, L.J., et al., 2007. Perinatal and childhood origins of cardiovascular disease. Int. J. Obes. (Lond) 31, 236–244.
Huang, R.C., Mori, T.A., Burke, V., Newnham, J., Stanley, F.J., Landau, L.I., Kendall, G.E., Oddy, W.H., Beilin, L.J., 2009. Synergy between adiposity, insulin resistance, metabolic risk factors, and inflammation in adolescents. Diabetes Care 32, 695–701.
Kaplowitz, P.B., Slora, E.J., Wasserman, R.C., Pedlow, S.E., Herman-Giddens, M.E., 2001. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics 108, 347–353.
Klumbiene, J., Sileikiene, L., Milasauskiene, Z., Zaborskis, A., Shatchkute, A., 2000. The relationship of childhood to adult blood pressure: longitudinal study of juvenile hypertension in Lithuania. J. Hypertens. 18, 531–538.
Lachos, V.H., Ghosh, P., Arellano-Valle, R.B., 2010. Likelihood based inference for skew-normal/independent linear mixed model. Stat. Sin. 20, 303–322.
Laird, N.M., Ware, J.H., 1982. Random-effects models for longitudinal data. Biometrics 38, 963–974.
Lett, H.S., Blumenthal, J.A., Babyak, M.A., Sherwood, A., Strauman, T., Robins, C., Newman, M.F., 2004. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosom. Med. 66, 305–315.
Licht, C.M., De Geus, E.J., Seldenrijk, A., Van Hout, H.P., Zitman, F.G., Van Dyck, R., Penninx, B.W., 2009. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension 53, 631–638.
Lu, X.Y., 2007. The leptin hypothesis of depression: a potential link between mood disorders and obesity? Curr. Opin. Pharmacol. 7, 648–652.
Lustman, P.J., Clouse, R.E., 2007. Depression in diabetes: the chicken or the egg? Psychosom. Med. 69, 297–299.
Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28, 412–419.
Mustillo, S., Worthman, C., Erkanli, A., Keeler, G., Angold, A., Costello, E.J., 2003. Obesity and psychiatric disorder: developmental trajectories. Pediatrics 111, 851–859.
Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J., Landau, L.I., 1993. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 342, 887–891.
Nicholson, A., Kuper, H., Hemingway, H., 2006. Depression as an aetiologic and prognostic factor in coronary heart disease: a meta-analysis of 6362 events among 146 538 participants in 54 observational studies. Eur. Heart J. 27, 2763–2774.
Oddy, W.H., Robinson, M., Ambrosini, G.L., Ta, O.S., De Klerk, N.H., Beilin, L.J., Silburn, S.R., Zubrick, S.R., Stanley, F.J., 2009. The association between dietary patterns and mental health in early adolescence. Prev. Med. 49, 39–44.
Pine, D.S., Cohen, P., Brook, J., Coplan, J.D., 1997. Psychiatric symptoms in adolescence as predictors of obesity in early adulthood: a longitudinal study. Am. J. Public Health 87, 1303–1310.
Pine, D.S., Cohen, P., Gurley, D., Brook, J., Ma, Y., 1998. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. Arch. Gen. Psychiatry 55, 56–64.
Porkka, K.V., Viikari, J.S., Taimela, S., Dahl, M., Akerblom, H.K., 1994. Tracking and predictiveness of serum lipid and lipoprotein measurements in childhood: a 12-year follow-up. The Cardiovascular Risk in Young Finns study. Am. J. Epidemiol. 140, 1096–1110.
R Development Core Team, 2007. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Richardson, L.P., Garrison, M.M., Drangsholt, M., Mancl, L., Leresche, L., 2006. Associations between depressive symptoms and obesity during puberty. Gen. Hosp. Psychiatry 28, 313–320.
Rugulies, R., 2002. Depression as a predictor for coronary heart disease. A review and meta-analysis. Am. J. Prev. Med. 23, 51–61.
Sawyer, M.G., Arney, F.M., Baghurst, P.A., Clark, J.J., Graetz, B.W., Kosky, R.J., Nurcombe, B., Patton, G.C., Prior, M.R., et al., 2001. The mental health of young people in Australia: key findings from the child and adolescent component of the national survey of mental health and well-being. Aust. N. Z. J. Psychiatry 35, 806–814.
Schulze, M.B., Kroke, A., Bergmann, M.M., Boeing, H., 2000. Differences of blood pressure estimates between consecutive measurements on one occasion: implications for inter-study comparability of epidemiologic studies. Eur. J. Epidemiol. 16, 891–898.
Shomaker, L.B., Tanofsky-Kraff, M., Young-Hyman, D., Han, J.C., Yanoff, L.B., Brady, S.M., Yanovski, S.Z., Yanovski, J.A., 2010. Psychological symptoms and insulin sensitivity in adolescents. Pediatr. Diabetes 11, 417–423.
Webber, L.S., Srinivasan, S.R., Wattigney, W.A., Berenson, G.S., 1991. Tracking of serum lipids and lipoproteins from childhood to adulthood. The Bogalusa Heart study. Am. J. Epidemiol. 133, 884–899.
Wulsin, L.R., Singal, B.M., 2003. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom. Med. 65, 201–210.
Zimmet, P.Z., Collins, V.R., Dowse, G.K., Knight, L.T., 1992. Hyperinsulinaemia in youth is a predictor of type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 35, 534–541.
Zubrick, S.R., Silburn, S.R., Gurrin, L., Teoh, H., Shepard, C., Carlton, J., Lawerence, D., 1997. Western Australian Child Health Survey: Education, Health and Competence. Australian Bureau of Statistics and the TVW Telethon Institute for Child Health Research, Perth, Western Australia.

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