

**Internalizing and Externalizing Behavior Problems in Childhood and Early Development
of Cardiovascular and Diabetes Risk: A Life Course Perspective**

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Abstract

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An accumulating evidence-base indicates that internalizing mental health disorders in adulthood are causally associated with cardiovascular diseases (CVD) and type-2 diabetes (T2DM). It is plausible, however, that the relationship between mental and cardiometabolic ill-health becomes established long before adulthood, and that externalizing problems (the other central domain of common psychopathology) are also involved. These questions, as well as questions on the mechanisms that underlie the relationships, have been insufficiently investigated.

The overarching goal of this dissertation was to expand current knowledge on how common mental health problems increase cardiometabolic risk over the life course.

First, the prospective association between childhood internalizing (emotional problems) and externalizing problems (hyperactivity and conduct problems) with CVD and T2DM risk in adolescence was assessed in data from the Avon Longitudinal Study of Parents and Children (ALSPAC, N=7,730). Results showed that hyperactivity problems were associated with insulin resistance (high HOMA-IR); that hyperactivity and conduct problems were each associated with high triglyceride levels; and that emotional problems were inversely associated with high triglyceride levels. These results suggest that childhood externalizing problems are an early life risk factor for CVD and T2DM and that childhood internalizing problems are not a risk factor or,

that risk in these children does not become apparent until after adolescence.

Second, the mechanisms underlying the prospective association of childhood hyperactivity and conduct problems with high levels of triglycerides in adolescence were investigated using causal mediation methods. Results showed that despite being associated with hyperactivity and with conduct problems, body mass index and lifestyle health behaviors including sleep, diet, physical activity, alcohol, and smoking, together these variables, as measured, mediated only 19.6% and 19.3% of the associations of hyperactivity and conduct problems with triglycerides, respectively. These results would suggest that mechanisms other than body adiposity and unhealthy behaviors are also involved and that those mechanisms have a larger role in mediating these relationships. Alternatively, it is possible that the observed small role of health behaviors is due to error in measurement and therefore improving measurements for health behaviors should be a central focus of future work.

Third and last, a systematic review of the literature on the relationship between childhood externalizing problems with CVD and T2DM risk was conducted. Studies were graded for propensity to bias. Evidence was summarized and assessed for consistency. Results strongly supported positive associations of externalizing problems with insulin resistance, T2DM, and with increased blood lipids among children and adolescents. Evidence suggested that associations are at least partly independent of body adiposity. Evidence provided mixed support for the associations with T2DM and blood lipids in adults and with other outcomes in children or adults. Studies in children tended to be cross-sectional and to use valid and reliable assessment methods, whereas studies of adults tended to be prospective and to rely on less-valid, less reliable assessment methods. These results warrant more research, specifically prospective studies that track children into young adulthood, that employ well-validated measures of externalizing behaviors, that rely

on repeated assessments of T2DM and CVD risk throughout follow-up, and that investigate mechanisms other than body adiposity and health behaviors.

Overall, this dissertation has found that childhood externalizing problems are prospectively associated with elevated CVD and T2DM risk, specifically with elevated risk of increased levels of blood lipids and insulin resistance. Unlike studies in adults, this dissertation does not support a role of internalizing problems as risk factors. Among children with externalizing problems, risk becomes evident before adolescence and appears to be largely driven by pathways independent of unhealthy behaviors and body adiposity. Implications of this research's findings for health practice were proposed. This dissertation identified several gaps and methodological shortcomings in the extant literature. Recommendations were made for future research, including fundamental next questions to investigate, and study designs and methodologies that are best suited to tackle those questions.

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Chapter 1:

Introduction

Background

Over the past decade, internalizing psychopathology diagnoses and behavioral symptomatology, including mood and anxiety disorders, have been singled-out as important contributors to the development and worsening of cardiovascular diseases (CVDs) and type-2 diabetes mellitus (T2DM) among adults¹⁻³. These mental health problems are highly prevalent. The National Comorbidity Survey (NCS-R) estimated the lifetime prevalence of anxiety disorders at 31 % and of mood disorders at 21 % in 2007. Prospective studies have shown associations of depression with incident coronary heart disease (CHD)¹, stroke⁴, and T2DM⁵, of generalized anxiety with CHD^{2,6-9}, and of post-traumatic stress disorder (PTSD) with incident ischemic heart disease (IHD)³, stroke³, and T2DM¹⁰.

CVDs and T2DM continue to be major causes of morbidity and mortality, worldwide and in the US¹¹, and these disorders and their biological precursors, once concentrated among older populations, are now increasingly diagnosed among the young¹². Currently, only a fraction of CVDs and T2DM are explained by known risk factors and the identification of new risk factors is a top and explicit priority of public health and medical research¹²⁻¹⁴.

Adults with depression, mood disorders, and other common psychopathology are much more likely than other adults to also have a positive life history of mental health problems starting in childhood^{15,16}. Cardiovascular and metabolic disorders have long latency periods, and their pathophysiological precursors are known to start developing early and have been described among young children^{17,18}. Thus, it is plausible that the relationships of internalizing problems/disorders with CVDs, T2DM and their precursors, extensively described among adults, are ones that are established in early life. However, very little research has examined these relationships among

youth.

A few studies that have examined and compared the roles of adolescence versus adult depressive symptoms in CVD development have shown that adolescence depressive symptoms influence adult CVD risk directly, that is, independently of their effect mediated by adult psychopathology¹⁹. These findings suggest not only that early life depressive symptomatology could be an independent CVD risk factor but also that these effects might become impervious to later improvements in mental health, underlying the importance of early detection of increased CVD risk and intervention among youth with behavioral problems.

Furthermore, while the role of internalizing psychopathology in CVD/T2DM risk has been extensively investigated, at least among adults, it remains unknown whether externalizing psychopathology (or impulse-control disorders) might also play a role. This is a glaring current gap in the literature given that externalizing disorders such as Attention-deficit Hyperactivity Disorder (ADHD) and Conduct Disorder are already known risk factors of obesity²⁰⁻²³, itself a strong precursor of CVD/T2DM, and that ADHD and Conduct Disorder are the two most commonly diagnosed mental health problems in children. In a 2015-16 survey 9 % of US children aged 3-17 years had received an ADHD diagnosis, and among those children, as many as half were found to have additional behavioral or conduct problems²⁴.

In addition to this paucity of evidence there are at least four additional limitations in our understanding of these relationships. First, it is not clear whether internalizing and externalizing problems or disorders are both similarly associated with CVD/T2DM risk, or whether risk is associated to certain specific domains of psychopathology or symptomatology. Internalizing-externalizing comorbidity is frequent in childhood and adolescence and very few studies have sought to discern potential specific associations. Unraveling these differences would be important

for clarifying who, among all youth with psycho-behavioral problems, might bear the highest CVD/T2DM risk, but also because knowledge of those distinctions could help shed important light into our still very poor understanding of the ways in which psychopathology brings about poor physical health.

Second, it is unclear when, throughout the life course, these relationship/s become evident. The processes that lead to the development of cardiovascular disorders are usually long, and the emergence of clinical signs is normally preceded by years of asymptomatic, subclinical accumulation of biological insults. Biomedical research has demonstrated that biological precursors of CVD/T2DM can be found in children as young age 5. Extensive evidence shows that early detection and intervention to stop these processes can have an impact in reducing morbidity and mortality, therefore identifying the developmental timing of the emergence of CVD and diabetes risk in children with internalizing/externalizing problems could therefore be critical for timely intervention.

Third, it is unclear whether any of these relationships may vary by sex. Given that prior and recent research in adult samples has found sex differences in the relationships of depression and anxiety with CVDs and T2DM^{19,25}, investigating in younger samples when such differences emerge is warranted. Identification of sex differences would help develop more valid estimates of effect sizes and would aid in the formulation of more efficient, sex-specific interventions to address risk.

Fourth, it is also not known what mediates the relationships between internalizing/externalizing problems and CVD/T2DM risk. Two overarching theories are proposed in the literature. The first posits that through persistent high levels of stress psychopathology may disrupt the body's stress-response systems –the SNS/HPA axis²⁶. Consequences to this disruption

include a cascade of neurochemical and neuroendocrine modifications that over time could lead to chronic high levels of inflammation and high levels of insulin. Chronic high levels of inflammation induce increases in blood lipids²⁷. Persistent high insulin would, in turn, also lead to development of insulin resistance, and high levels of insulin and glucocorticoids are known to be key contributors to atherogenic processes in coronary arteries²⁸. The alternative theory posits that stress-related psychopathology influences CVD/T2DM risk mainly by mechanisms involving unfavorable health behaviors²⁶, specifically, behaviors known to increase CVD/T2DM risk through obesogenic effects --poor diet²⁹, poor sleeping habits³⁰, sedentary lifestyle²⁰-- and by stress-coping, and sensation-seeking behaviors such as cigarette smoking, and alcohol use³¹.

Identifying what the specific mechanisms are would contribute knowledge that could be critical in informing potential avenues for intervention by targeting of specific mediators but would also significantly strengthen the case of a causal link between these associations.

Identifying whether the association/s are substantively independent of pathways that involve increased body adiposity could have significant implications for medical practice. By current clinical guidelines CVD/T2DM risk factors are assessed only among children/adolescents with diagnosed overweight/obesity. If the relationships between internalizing/ externalizing psychopathology and CVD/T2DM risk are only partially mediated by body adiposity then a sizable proportion of the children with these behavioral problems --those with body mass index within normal ranges- might be children with elevated, but unidentified and unaddressed, elevated CVD/T2DM risk.

Dissertation overview

The overarching goal of this dissertation is to expand our current understanding of the role of childhood and adolescence externalizing and externalizing behavior problems/disorders in the development of CVD and T2DM risk over the life course.

Specifically, I examine, whether childhood internalizing and externalizing behavior problems prospectively predict increased levels, in late adolescence, of 3 risk markers proven to be causally related to Ischemic heart disease, stroke, and T2DM (**aim 1**); I assess, using causal mediation methods, the mechanisms underlying the prospective associations of childhood behavior problems with CVD/T2DM risk, estimating indirect effects (NIE) mediated by diet, sleep, physical activity, smoking, alcohol use and body mass index, as well as direct or no mediated- effects (NDE) (**aim 2**); and I conduct a systematic review of the extant literature that investigates the relationship of childhood externalizing disorders with increased CVD/T2DM throughout the life-course for evidence of associations, developmental timing of the emergence of risk, and for evidence that these associations are, at least partially, independent of increased body adiposity (**aim 3**).

This dissertation is structured into 5 chapters. **Chapter 1** features this introduction.

Chapter 2 features research assessing **aim 1**, conducted using data from a large, prospective, UK-based birth cohort, the Avon Longitudinal Study of Parents and Children. I assess associations between children's age 4 and age 7 internalizing problems (emotional problems) and externalizing problems (hyperactivity, and conduct problems) with clinically high levels of insulin resistance (HOMA-IR index), LDL-Cholesterol, and triglycerides. These associations are examined in models that adjust different behavior problems for one another and also for a wide range of confounding factors including demographic, socioeconomic, maternal and environmental factors, family history of CVD and T2DM, pregnancy and birth outcomes, and breastfeeding. I use

inverse probability of censoring weights to further control for attrition bias.

Chapter 3 features research assessing **aim 2**. The mechanisms underlying associations identified by aim 1 research are examined. Using state of the art causal-mediation methods, indirect effects, defined as the effects that work through pathways involving health behaviors and BMI, and direct effects, defined as all other pathways not involving those mediators, are determined. The relative contribution of those pathways to the total effects of hyperactivity and conduct problems on triglycerides, are also estimated.

Chapter 4 presents research that addresses **aim 3**, featuring a systematic review that assesses the existing literature for consistency with regards to three key questions: 1) What is the evidence of a positive association between childhood and/or adolescence externalizing behaviors/psychopathology and CVD/T2DM risk, 2) What is the developmental timing (childhood, adolescence, young adulthood, later in life) of the emergence of heightened risk, and 3) What is the evidence and the degree to which the relationship/s are independent of body adiposity.

Chapter 5 features the conclusions of this dissertation where results from chapters 2-4 are integrated and discussed in the context of existing research and the goals of this dissertation.

Altogether, the research conducted in this dissertation could advance knowledge in several important fronts and have an impact on health practice. Given that internalizing/externalizing psychopathology and cardiometabolic disorders are main drivers of global disease burden, unraveling whether and how they are causally linked since childhood could potentially open new avenues of intervention with, potentially, a sizable impact in life-course health and population disease burden. By directly exploring the role, in causal pathways, of factors that are modifiable, and by using exposure and outcome definitions with clinical meaning, this research could provide

knowledge readily applicable to research on public health intervention. That mental and cardiometabolic ill-health are mainly linked through biological (i.e not through health behaviors) pathways is plausible and is a current research question with implications for prevention strategies. This dissertation could also contribute important knowledge to this nascent and important line of inquiry.

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Chapter 2:

Childhood Internalizing and Externalizing Behavior Problems and Cardiovascular and Diabetes Mellitus Risk in Adolescence

Abstract

Common psychopathological disorders, including depression and anxiety, are known risk factors of cardiovascular disease (CVD) and Type-2 Diabetes Mellitus (T2DM) in adults. Because cardiovascular and metabolic disorders have in general long latency periods and psychopathology tends to track from childhood into adulthood, it is possible that these relationships are established early in life, but very little research has examined these questions. Using data from a large British birth-cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC, N=7,730), I examined the relationship between measures assessing internalizing and externalizing behavior problems -the two overarching domains of common childhood psychopathology- with elevated risk of CVD and diabetes in late adolescence. Using parents' ratings of their children's behavior at ages 4 and 7 (Strengths and Difficulties Questionnaire), I assessed whether externalizing problems (hyperactivity and conduct problems subscales) and internalizing problems (emotional problems subscale) predicted the level of markers of CVD and T2DM risk: triglycerides > 130 mg/dl, LDL-cholesterol > 130 mg/dl, and insulin resistance (Homeostasis model assessment of insulin resistance > 2.9, at age 17). After accounting for attrition bias and adjusting for demographic, socioeconomic, maternal factors, pregnancy and birth outcomes, and early childhood factors, I found positive associations of insulin resistance with hyperactivity (RR= 1.28, 95% CI= 1.01-1.61); of high triglyceridemia with both hyperactivity (RR= 1.61, 95% CI=1.24-2.09) and conduct problems (RR= 1.51, 95%CI= 1.20-1.90); and an inverse association of high triglyceridemia with emotional problems (RR= 0.64, 95% CI= 0.42-0.97). This research suggests that childhood externalizing problems might be an early life risk factor for CVD and T2DM and also suggests that childhood internalizing problems are either not a risk factor for early

cardiovascular and diabetes risk or, that risk in these children does not increase until after adolescence. More research is needed to confirm these findings and to determine mechanisms involved in these effects.

Introduction

Adults with common psychopathology such as mood disorders, including depression and anxiety, are at an increased risk of CVD and T2DM¹⁻¹⁰. Longitudinal studies have shown associations of depression with incident coronary heart disease (CHD)²⁻⁴, stroke¹⁰, and T2DM¹¹, of generalized anxiety with CHD⁵⁻⁹, and of posttraumatic stress disorder (PTSD) with incident ischemic heart disease (IHD)¹², stroke¹², and diabetes¹³. Much less research, however, has investigated the role of common psychopathology in children on CVD/T2DM risk, beyond its association with body adiposity¹⁴. Common childhood psychopathology is linked to adult psychopathology^{15,16}. Cardiovascular and metabolic diseases have in general long latency periods and their pathophysiological precursors are known to start developing during childhood^{17,18}. Therefore, it is possible that the relationships between psychopathology and CVDs and T2DM, extensively described among adults, are ones that are established in early life.

Within that framework, it is likely that at least some of the relationships thus far described between adult psychopathology and CVD/ T2DM risk could indeed be explained by a history of childhood psychopathology. That is, it is plausible that childhood common psychopathology is a childhood risk factor with direct and indirect effects on adult CVD/T2DM risk, where the indirect effects are mediated, in part, by adult psychopathology. This hypothesis has found some support in a recent prospective, population-based study¹⁹ that estimated adult CVD risk in relation to psychological distress. The investigators found that psychological distress throughout the life course was associated with greater adult CVD risk. Specifically, they reported that, compared with CVD risk in participants with no history of psychological distress, CVD risk was the greatest among participants who had persistent psychological distress (childhood-through-adulthood),

followed by CVD risk among participants with childhood-only and adulthood-only psychological distress, in that order.

In addition to a general paucity of evidence, there are at least three additional limitations in our understanding of the relationship between childhood behavior problems and CVD/T2DM risk. First, we don't know when, in the life course, the relationship starts. Very few studies have examined CVD risk before adulthood and the very few studies that did either used cross-sectional designs²⁰⁻²⁵ or very small ^{21,23,25} and selected samples²⁰⁻²², such as obese adolescents. This is an extant question in the current literature with critical implications for screening and primary prevention efforts. Second, we don't know whether this is a general effect that cuts across all domains of psychopathology or whether this is one that pertains to only certain domain problems. Answering this question could bring important insight to our still poor understanding of the neurobiology^{26,27} underlying psychopathology²⁸ and processes of biological embedding of psychopathology. Finally, it has never been examined whether these associations vary by sex. Given that prior and recent research in adult samples has found sex differences in the relationships of depression and anxiety with CVDs and T2DM, investigating in younger samples when such differences emerge is warranted. Identification of sex differences is important for two reasons: first, to obtain more valid estimates of effect sizes, and second, because we may gain important insight into still unknown sex divergences in pathobiological pathways.

Very few prospective studies have examined CVD/T2DM risk before adulthood in relationship to childhood common psychopathology. In one large, longitudinal, population-based study¹⁴, boys with behavior problems throughout childhood had smaller –not larger- increases in blood pressure from childhood to adolescence. But, also in this study, behavior problems at age 14 were cross-sectionally associated with higher HOMA-IR values (girls only), higher levels of total

cholesterol (boys only), and higher triglycerides levels (boys and girls).

Common psychopathology in childhood refers to a set of behavioral disturbances observable to parents and teachers that are broadly organized into two distinct domains, internalizing and externalizing behavior problems²⁹⁻³¹. Internalizing behavior problems are manifested inwardly, and include depressive, anxious, and withdrawal symptomatology. Externalizing behavior problems are manifested outwardly, are characterized by poor self-regulation and impulsivity and include hyperactivity, inattention, and antisocial and disruptive behaviors.

In this study, I separately examine the longitudinal relationship of childhood internalizing and externalizing behavior problems, with CVD and T2DM risk in late adolescence. I assess CVD and T2DM risk using measures of biological precursors proven to be causally related to Ischemic heart disease, stroke, and T2DM: 1) insulin resistance (IR), 2) high triglyceridemia, and 3) elevated blood levels of LDL-cholesterol^{32,33}. I assess for sex differences in the relationships and I examine the extent to which main effects are mediated by an effect of behavior problems on BMI in mid-adolescence. I examine these questions using a prospective study design and data from a large, population based, transgenerational birth cohort study, established in 1990 in the UK.

Methods

Setting and participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large, population-based, cohort study in the UK³⁴. The study recruited pregnant women in the Avon county of the Bristol area with expected due dates between April 1, 1990 and December 31, 1992. From those pregnancies, 13,978 children remained alive by year 1. From study initiation, 1990-92, to 2012, 68 assessments had been administered in relation to the children (from birth to age 18), including 25 child-based questionnaires, 34 child-completed questionnaires, and 9 clinical assessments (“Focus clinics”), starting at age 7. Of the study core sample (n=13,978), 7,730 children had complete questionnaire data on internalizing and externalizing problems both at ages 4 and 7 years (exposure of interest) and constitute this study’s analytical sample. CM risk measures (study outcomes) were assessed at both the clinic visits at ages 15/16- and 17/18-years old. Some children attended both clinics and some children attended one of them. Age 17 assessments were used in these analyses whenever available (72% of the children) and age 15 measures were used otherwise (28%). Out of 7,730 children in the analytical sample, n=3,422 (44%), had available measures of fasting insulin and glucose, and n= 3,446 (45%) had available measures of blood lipids. To account for possible biases created by this follow-up attrition all analyses are adjusted by inverse probability of censoring weights (IPCW), whereby each participant was assigned a weight corresponding to the probability of that participant remaining in the study based on her/his exposure (behavior problems), and covariates status. A comparison of variables distribution between participants retained and lost to follow-up is shown in the appendix tables, A.2.1 and A.2.2. Compared with retained participants, participants lost to follow-up were slightly more likely

to have an externalizing problem, come from households with lower income, and have mothers of lower educational attainment.

Measures

Internalizing and externalizing behavior problems

Behavior problems in the participants were assessed using the parent version of the Strengths and Difficulties (S&D) questionnaire³⁵ completed by the mothers or main caregivers at participant's ages 4 and 7 years. The S&D is one of the most widely used short questionnaires for the evaluation of child mental health problems in epidemiological samples in children aged 4-16 years of a wide range of socio-economic status. It consists of 25 items (each querying on a specific behavior) organized into 5 subscales, two assessing internalizing behaviors ("emotional problems" and "peer problems"), two assessing externalizing problems ("hyperactivity problems" and "conduct problems") and a last one not assessing a behavior problem. Parents rated their child's behavior over the past 6 months on a 3-point scale: Not true, Somewhat true, and Certainly true. The total difficulties score (sum of scores from the four subscales that indicate a difficulty) is considered a valid measure of overall child psychopathology³⁵. The score correlates well with interview measures, differentiates clinical from community samples, and correlates with clinician-rated and diagnosed behavioral psychopathology. Reliability of the S&D scale was deemed satisfactory when assessed in a nationally representative sample of British children aged 5-15 years, N=10,438, with mean Cronbach's alpha across subscales equal to 0.73, and mean test-retest reliability after 4-6 months across subscales equal to 0.62³⁶.

Scoring of the S&D questionnaire: Most items in the scale are scored 0=Not true, 1=Somewhat

true, and 2=Certainly true. Five items are reverse coded. Scores for each of the subscales are obtained by summing the scores of each of the 5 items that make up the subscale. Scores for subscales have therefore a range 0-10. Cut-off points for each of the four subscales of behavior problems have been defined using a large, representative sample of British children. For each subscale, the cut-off points divide the categories “Close to average” (bottom 80%), “Slightly raised” (10%), “High”, (5%) and “Very high” (5%)³⁷. For these analyses, I created four binary variables, 1) Ever emotional problems, 2) Ever peer problems, 3) Ever hyperactivity problems, and 4) Ever conduct problems, each reflecting whether the specific behavior problem was present (high or very high scores, based on above defined categories) at either age 4 or age 7 assessments.

Cardiovascular and T2DM risk markers

Study participants provided fasting blood samples at one, or both, of 15/16-years old clinic visit and the 17/18-years old clinic visit. Teens were instructed to fast overnight if attending the clinic in the morning or for 6 hours at least if attending after lunch. Blood samples were processed immediately after collection and plasma was frozen at -80°C until assay time, between three to nine months later, with no freeze-thaw cycles in between. A modified version of the standard Lipid Research Clinics Protocol that employs enzymatic reagents was used to determine blood lipid concentrations (total cholesterol [Total-C], high density lipoprotein cholesterol [HDL-C], and triglycerides). LDL-C was determined from these by applying the Friedwald formula: $\text{LDL-C} = \text{Total-C} - \text{HDL-C} + \text{Triglycerides} \times 0.45$. Insulin was measured by means of ELISA (Enzyme linked immunosorbent assay; Menodia, Uppsala, Sweden) that did not cross-react with proinsulin. Glucose was measured using an automated procedure. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR index). The HOMA-IR index has

been used extensively. It has been validated against gold-standard methods including the hyperinsulinemic- euglycemic clamp³⁸. HOMA-IR is calculated as: fasting insulin [uU /mL] x fasting glucose [mmol /L] / 22.5. Currently, there is no consensus on a cut-off point to define high values of HOMA-IR in adolescents; therefore, for analyses, HOMA-IR was dichotomized at the 85th percentile point for the sample distribution, corresponding to an index value of 2.9. This study-specific cut-off choice is supported by a recent study of 667 healthy Chilean adolescents, in which a value of HOMA-IR of 2.6 (84th percentile point of the sample distribution) was identified as the optimal cut-off point for diagnosis of the Metabolic Syndrome, by ROC analysis³⁹. The positive relationship of blood levels of LDL-C and of triglycerides^{33,40,41} with risk of coronary heart disease and other cardiovascular outcomes have been very well documented. Both markers are routinely assessed in the clinical setting as indicators of elevated cardiovascular risk among healthy adults. For these analyses, both LDL-C and triglycerides were dichotomized as “High” (≥ 130 mg/dl) versus “Not high” (< 130 mg/dl), as recommended by the National Health of Blood and Lung Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents⁴², 2012, for children ages 10-19 years. Height and weight were assessed at the clinic visit at age 15/16, with children wearing light clothes and no shoes. Weight was assessed using Tanita scales and was recorded to the nearest 0.1 kg⁴³ and height was assessed with a Harpende stadiometer and recorded to the nearest 0.1 cm. BMI was calculated as weight (kg)/ height (cm)² and for analysis BMI was dichotomized around the CDC-estimated 95th percentile point of BMI for sex and age (in months) that separates obese and non-obese children.

Study covariates

All information on study covariates was collected before a participant’s age 4, the first

assessment of behavior problems. Most Information was collected by means of mother-completed questionnaires or was extracted from routine antenatal medical records of mothers who granted access to the records. Information reported by mothers through questionnaires during pregnancy included: child's ethnicity (White/Caucasian or other), maternal highest educational attainment (Below O-level=less than high school diploma, O-level =high school diploma, A-level = post high-school education), number of previous pregnancies, whether mother's biological parents had any of diabetes (Yes, No), hypertension (Yes, No), and heart disease (Yes, No). Information collected from the mothers by questionnaire after birth and before child's age 4 included: maternal diagnosis of diabetes (never, ever, during pregnancy only), breastfeeding, (never, < 3 months, 3-5 months, 6+ months), maternal depression (Assessed by the Edinburgh Post Natal Depression Scale, previously validated in ALSPAC; the total score was used in these analyses); household weekly income (less than £100, £100-199, £200-299, £300-399 and £400+), and neighborhood stress. The neighborhood stress index (0-22) was determined based on mother's answers to 11 questions about housing and neighborhood conditions. Information extracted from antenatal medical records included: maternal age at delivery, gestational hypertension (Yes, No), and weight gain through pregnancy (less than, recommended, or above recommended, according to Institute of Medicine recommendations for weight gain in pregnancy based on the mother's weight before pregnancy), maternal diagnosis of diabetes (never, before pregnancy, during pregnancy). Measures of birth weight and gestational age were also extracted from these records and used to derive birth-outcome variables: "Preterm, Yes/No" (defined around the CDC-defined cut-off point of 37 weeks), "Small-for-gestational-age (SGA)", Yes/No, and "Large-for-gestational-age (LGA)", Yes/No, based on CDC-provided cut-offs points of birth weight (in grams) for gestational age (in weeks). These covariates were chosen based on prior literature indicating that they were risk factors of

child behavior problems or CM risk.

Missing covariate information

The proportion of missing covariate information was typically below 5% and was the greatest for family income at 13%. Missing covariate information was assumed to be at random and was imputed using *IVEware* software. The software was developed following the implementation⁴⁴ of the multiple imputation framework which uses a Bayesian approach for estimating missing values. Inferences resulting from analyses run separately in each of the imputed datasets (5) were combined to produce summary effect measures and covariance matrixes with SAS proc mianalize.

Censoring weights

Approximately 55% of the cohort left the study between recruitment and the year 2012. To account for possible biases due to study attrition over the 10-year follow-up, analyses were adjusted using inverse probability of censoring weights (IPCW)⁴⁵. Separate sets of stabilized censoring weights (SCW) were estimated for different study sub-samples for the different study outcomes (insulin resistance, triglycerides, and LDL-C). Weights were estimated as follows: for each study outcome I created a binary variable to indicate censoring (0=Outcome information available, 1=No outcome information available). I fitted logistic regression models to estimate the unconditional and conditional probabilities of remaining uncensored (C=0) using behavior problem variables and study covariates as predictors of censoring status. SCW were calculated as: $= P(C=0) / P(C=0 | E, Cov)$, where “E” represents eight variables reflecting the status (Yes, No) on each of the four subscales indicating a behavior problem at ages 4 and 7 years, and “Cov”

represents all study covariates assessed before age 4. In each of the estimated SCW sets, the mean SCW was in the 0.999 -1.000 range and the largest range of weights in a given set of SCW was 2.1.

Analytical approach

I first examined whether ever having a behavior problem –hyperactivity, conduct, emotional, or emotional problems- was associated with the study outcomes using Chi-Square tests. I then calculated the relative risk associated with each behavior problem for each outcome in multivariate log-linear regression models, separately for each behavior problems. Models were progressively adjusted for confounding using the same general strategy for all outcomes, though the actual covariates included varied slightly across outcomes as not all covariates were found to confound the main effects of all the outcomes. Covariates were considered confounders and were kept in the models if, when introduced to the models, the observed change in the beta coefficient associated with the main effect was of 10 % or more. In Model 1 I adjusted for sex and race, model 2 added additional demographics, maternal characteristics, and family history of CM disorders, and model 3 added pregnancy and gestation-level covariates, birth outcomes, and breastfeeding. To determine whether the effects of behavior problems on CM risk markers varied by sex an additional model (Model 3b) added the sex*behavior problems effect modification term to the fully adjusted model 3. In model 4, to examine whether the effects of behavior problems on CM risk were explained by an effect of the behavior problems on obesity, which in turn influenced CM risk at age 17, I added obesity at age 15 to the fully adjusted Model 3. In this stage, when I found that a main effect was reduced upon further adjustment of the model for BMI, I interpreted the change as an indication that obesity at age 15 might be in a pathway linking the childhood

behavior problems with the CM risk marker at age 17. This interpretation of regression results requires the absence of statistical interaction between the variable for the behavior problems and the BMI variable. I assessed the presence of such interactions (I had adequate power), using a 0.10 significance level. No interactions were detected. All tests conducted in these analyses, including bivariate association tests and regression models, are adjusted by means of IPCW to account for the effects of participant attrition through study follow-up. All statistical analyses were conducted with SAS 9.4.

Results

Description of the cohort

The distribution of study variables among participants is shown in table 2.1. In this study sample, 11% of the participants had hyperactivity problems at ages 4, 7, or at both ages, while 17% had conduct problems, and 9% had emotional problems. Among these children, 15% went on to have a HOMA-IR index above 2.92 in late adolescence, while 3% of them had fasting LDL-C levels above 130 mg/dl, and 11 % of them had triglyceride levels above 130 mg/dl.

Behavior problems and outcomes

In bivariate analyses that assessed crude associations between each behavior problem and the study outcomes (Table 2.1), hyperactivity problems were associated with high HOMA-IR index (13.9% versus 10.1%, $p= 0.01$), and with high triglycerides (16.4% versus 9.9%, $p < 0.00$). Conduct problems were associated with high HOMA-IR index value (19.1% versus 16.2%, $p= 0.10$), and were associated with high triglycerides (23.3% versus 16.0%, $p < 0.00$). Emotional problems were not associated with high HOMA-IR index value, or with high LDL-C, but were negatively associated with high triglycerides (5.8% versus 9.1%, $p= 0.04$). PPs were not associated with any study outcomes.

Bivariate tests also showed that hyperactivity and conduct problems were positively associated with obesity at age 15 (hyperactivity: 15.4% versus 11.4%, $p= 0.020$; conduct problems: 25.3% versus 18.0%, $p < 0.001$), while emotional problems were not associated with obesity (emotional problems: 7.3% versus 9.6%, $p=0.14$). In turn, obesity was a strong and significant

predictor of high HOMA-IR index 15.8% versus 3.1%, $p < 0.001$, high LDL-C (11.8% versus 3.6%, $p < 0.001$), and high triglycerides (16.7% versus 4.0%, $p < 0.001$) (Table 2.1).

In multivariate log-linear regression models that estimated the relative risk for the study outcomes associated with each behavior problems (Ever behavior problem versus Never behavior problem), progressively adjusting for demographic, familiar and maternal risk factors of cardiovascular and diabetes risk, maternal mental health, pregnancy and birth outcomes, and early-childhood confounder variables, high HOMA-IR index and high triglycerides remained associated with hyperactivity problems (high HOMA-IR index, $RR=1.28$, 95% $CI= 1.01 - 1.61$, Table 2.2; high triglycerides levels, $RR=1.61$, 95% $CI= 1.24 - 2.09$, Table 2.4), and high triglycerides remained associated with conduct problems ($RR=1.51$, 95% $CI= 1.20 - 1.90$, Table 2.4) and were negatively associated with emotional problems ($RR=0.66$, 95% $CI= 0.42 - 0.99$, Table 2.4). There were no associations of high LDL-C with any behavior problems after confounder adjustment (Table 2.3). I did not find statistical evidence of sex differences in the associations of study outcomes with behavior problems (Tables 2.2-2.4). Further adjustment of full-models by adolescence BMI led to only minimal reductions in the estimations of effect size.

To rule out the possibility that the differences in triglycerides and LDL-C levels between children with and without behavior problems observed at the end of follow-up could have already been present at start of study follow-up, a secondary analysis (not shown) was conducted on a subset of children ($N= 2353$) for whom measures of non-fasting lipids were available from the clinic at age 7 (study baseline point). Neither the levels of triglycerides nor LDL-C levels at age 7 were associated with any of the behavior problems assessed.

In sensitivity analysis I further adjusted models for use of oral contraceptives, which are known to elevate triglycerides and LDL-C. There were no differences in the rates of contraceptive

use between girls with and without behavior problems. Adjusting models for contraceptive use did not materially change the results.

Discussion

I studied whether externalizing and internalizing problems in childhood predicted elevated CVD and T2DM risk, the latter indicated by clinically significant levels of three biological precursors of these outcomes –high triglycerides, high LDL-Cholesterol, and insulin resistance- in late adolescence, using a large, population-based sample. I found positive associations of externalizing problems with insulin resistance and triglycerides, and null or inverse associations of internalizing problems with these outcomes. Some of the associations, which were notably stronger for triglycerides, persisted after adjustment for demographic, socioeconomic, maternal and environmental factors, family history of CVD and T2DM, pregnancy and birth outcomes, and breastfeeding. The association was also evident when I examined triglyceride levels as a continuous outcome (results not shown). In fully adjusted models, hyperactivity was associated with an 8% increase in triglycerides ($p < .01$) while conduct problems were associated with a 5% increase ($p < .01$). I did not find evidence of sex differences in the associations examined and found that obesity at age 15 only minimally explained the relationships between externalizing problems and the study outcomes at age 17. To my knowledge, this is one of the first studies to prospectively examine both internalizing and externalizing problems in relation to CVD and T2DM precursors, other than body adiposity, before adulthood.

The positive associations of externalizing problems with insulin resistance and triglycerides reported here are novel, as these relationships have not been prospective examined

before, but are consistent with findings, in a community sample, of cross-sectional positive associations of CBCL-aggressive behavior scores at age 14 with higher triglycerides (in boys and girls) and with higher HOMA-IR values (in girls only). The positive association of externalizing problems with obesity has however been described quite extensively, mostly among adults⁴⁶⁻⁴⁸, but also in children^{31,46-48}, and is summarized in systematic reviews and meta-analyses⁴⁹. Our findings are largely consistent with that research. For example, a cross-sectional positive association of externalizing problems with obesity was found in a community-based, study of 5-year old children³¹. In another study ADHD at age 10 was associated with BMI at age 14⁴⁸, while in another prospective study, hyperactivity and conduct problems at age 5 did not associate with BMI at age 10 (appraised by mothers) but predicted higher BMI at age 30.

My results in relation to internalizing problems are less consistent with the current literature. The finding of a null association between emotional problems and insulin resistance in both sexes contradicts the reported positive association of depression with insulin resistance and with incident diabetes reported in studies of adults,^{11,50,51} an association that also appears to be limited to women^{26,27}. However, there are fewer studies that have examined the relationship among children, and there is less consistency^{14,18,22,52,53} among these studies. Of five prior studies, just one used a prospective design and a community sample⁵⁴, and that study found, like I did, a null association of depressive symptoms with insulin resistance. The other four studies^{14,24,52} reported positive associations but, three of these studies were cross-sectional, and the fourth was a longitudinal study²⁰ of overweight or obese children with high HOMA values at baseline. It is possible that depression is prospectively associated with insulin resistance, but the relationship is one that does not develop before adulthood. Among children, insulin resistance almost always develops in the context of overweight or obesity. These children may develop depressive

symptoms subsequent to perception of peer rejection or social stigma related to their excess weight, which would explain the positive association reported by all cross-sectional studies and by the longitudinal study of overweight/obese children who had high levels of HOMA-IR index at baseline.

My finding of an inverse association of internalizing problems with triglycerides in adolescence is also novel, as no other studies have examined this relationship in childhood using a longitudinal design. The result seems at odds with the extended literature that has examined the relationship of depression and CVD/T2DM risk factors in samples of adults⁵³. The finding is, nevertheless, internally consistent with my other observation of an inverse association of internalizing problems with obesity. The literature that delves into this relationship among children is, however, sparse, and quite inconsistent, with some studies finding, like us, inverse associations. For example, a study that reported a positive¹⁴, cross-sectional association of depressive symptoms with triglycerides at age 14, also found a prospective inverse association of depressive symptoms at age 5 with systolic blood pressure at age 14, the latter examined using a prospective design and follow-up similar to ours. Both those study's observations were apparent only among boys.

My finding of an inverse association of internalizing problems with obesity is also at odds with the widely reported positive association observed among adults (likely, mostly among women) but it is in agreement with at least two prior studies in children. In one of them that, like us, examined a large population-based British sample, the British Cohort Study⁴⁶, emotional problems at age 5 were inversely associated with obesity at age 10. The other study, by Suglia et al.³¹, observed, in a large community sample of children of age 5, a cross-sectional negative association of internalizing problems with obesity (the association was negative among boys and null among the girls). These apparent discrepancies between studies in adults and children may

make sense in light of research showing that while depression is associated with increased eating (one of the key drivers of obesity) among adults, in children, depressive symptoms are associated with appetite suppression^{55,56}.

Although I observed, as expected, sex differences in the prevalence of behavior problems and of high LDL-C, I did not find statistical evidence of sex differences in any of the associations examined. It is possible that sex differences in these associations become statistically different after adolescence.

Together, the evidence from our study and prior studies seem to suggest that the nature of the relationship of depression/depressive symptoms and obesity and CVD/T2DM risk might be a complex one, one that may change direction over the life course, and with changes operating differently across the sexes. Even though the number of studies among youth is still small, the evidence seems to indicate that while depression and depressive symptoms positively predict obesity and higher CVD and T2DM risk in adult women, the relationship could be null or inverse in childhood, with unclear sex differences before adulthood.

Several mechanisms could underlie the associations reported in this study. Although current empirical evidence is insufficient, it is speculated, as briefly mentioned above, that at least some of these associations are driven by an effect of behavior problems on diet and eating behaviors. Externalizing problems are associated with greater impulsivity, and low inhibitory control and self-regulation. Impulsiveness may lead to binge eating. Higher-than expected rates of binge eating have been observed in ADHD^{57,58}. Impulsiveness and lack of self-control may promote the ingestion of large quantities of comfort foods⁵⁹, including sugar-sweetened beverages and junk food with high content of trans-fats, both linked with increased CVD/T2DM risk through direct effects and indirect effects mediated by body adiposity. Internalizing symptoms have, on the

other hand, been associated, among children, with appetite suppression, which would be consistent with the inverse association found for emotional problems with obesity and triglycerides.

The associations of behavior problems with high HOMA-IR index and with high triglycerides were incompletely explained by an effect of behavior problems on BMI, suggesting the existence of direct and/or alternative, indirect pathways. Impulsiveness has been shown to increase triglyceride levels, independently of BMI⁶⁰. Sleep disturbances have been shown to negatively affect cardiovascular risk and to do so only in part by influencing BMI. It is possible that different sleep disturbances associated with externalizing^{61,62} and internalizing behavior problems—with reduced sleeping associated with externalizing, and increased sleeping associated with internalizing problems—could explain some of the associations reported by this study. Physical activity is another factor known to be related to behavior problems in children that could impact CVD and T2DM risk directly and indirectly through BMI. Tobacco smoking is yet another mechanism possibly involved in these relationships. Smoking is associated with elevated levels of triglycerides, in both sexes, particularly in males^{63,64}. On the other hand, childhood externalizing problems have been shown to be positively, while internalizing problems are inversely associated with smoking in adolescence⁶⁵. Therefore, smoking could explain the positive and inverse relationships found for externalizing and internalizing problems respectively with triglycerides. Finally, mechanisms other than health behaviors could be involved as well.

This study had a number of limitations. First, as in most longitudinal studies, this study suffered from participant attrition; we lost approximately 50 percent of children over the 10-year follow-up period. However, we addressed this by using IPCW to account for at least some of the bias that may have been created by attrition.

Second, I relied on screening questionnaires to determine childhood behavior problems

rather than on clinical interview diagnosis, which is considered the gold standard for assessment. In fact, it is possible that the negative association that I, and others, have found for internalizing problems and some study outcomes could be the result of error in the assessment of internalizing symptoms. It has been observed by others that findings involving internalizing problems in young children tend to be less consistent than findings involving externalizing problems, and it has been proposed that this could result from young children's difficulties with expressing emotions and their parents' difficulties with correctly understanding those expressions and withdrawal behaviors in general⁶⁶. However, such assessment errors would be expected to bias an effect size to -and not away- from the null, as I have observed for some of the relationships examined. An alternative explanation could be that parents of children with less-than-average appetite and lower BMI are more likely to interpret the lack of appetite as an indication of emotional problems in the child (reverse causation). This seems unlikely, however, as the scales have been extensively validated and the cut-off points that I used have been determined against clinical interview diagnosis in a large, sample of British children –as was this study's sample- and cut-offs were deemed appropriate for children ages 4-16.

Third, I did not have baseline measures of one of the study outcomes, HOMA-IR index, and had baseline triglycerides and LDL-C measures for a fraction of participants; therefore, it is possible that differences observed at age 17 were already present at baseline. However, this is unlikely given the young age of the children at baseline, the long follow-up period, and particularly, because baseline triglycerides and LDL-C levels did not vary by behavior problem status among the 68% for whom those measures were available. As in every observational study, this study may suffer from residual confounding bias due to unmeasured confounders, or error in the assessment of confounders. For example, I did not adjust for use of psycho-stimulant drugs,

such as methylphenidate, which some of the children with externalizing disorders may have been using. These drugs have been shown to reduce levels of triglycerides⁶⁷, therefore, our results are biased to the null and our effect estimates are conservative. It's been reported that approximately 0.2 % of the UK population of children aged 15-19 y used methylphenidate in the year 2005, when this study's outcomes were assessed, and the percent doubled by year 2012. In the US, 3.3 % of children in that age group⁶⁷ used methylphenidate in 2012. The relationship of externalizing problems with triglycerides might vary across countries with different prevalence of methylphenidate use.

This study examined only three of the most relevant precursors of CVD and T2DM and these results now warrant extending this research to investigate other key cardiometabolic outcomes including blood pressure, carotid atherosclerosis, and others. A few prior studies that have examined the association of behavior problems with blood pressure in pediatric samples⁶⁸⁻⁷¹ have found null associations⁶⁹⁻⁷⁰ or associations that suggest a protective effect of behavior problems^{68,71}. Those relationships appear to be stronger among boys, and in particular among boys with more severe externalizing symptoms. Future studies that investigate blood pressure in relation to childhood behavior problems should use study designs that are appropriate to assess and disentangle the roles of these factors.

The associations I estimated are only moderate in size, but these effects could contribute to overall population burden of chronic diseases significantly given the high prevalence of externalizing problems and considering that I assessed early effects but these relationships are thought to operate through cumulative effects over the life course leading to significantly higher risk in adulthood.

The sample of this analysis was overwhelmingly white and more affluent than the source population, and therefore the findings reported here might not be generalizable to other populations.

This study also has important advantages. First, it draws from a large and well-established birth-cohort known for the quality and completeness of its measures and intensive follow-up. Second, like only very few prior studies have done, I was able to examine longitudinal effects of both dimensions of childhood behavioral psychopathology. Third, by relying on two separate assessments of children's behavior problems I was able to identify both, childhood early and later onset cases. Fourth, I was able to adjust for confounding in a more comprehensive way than most other studies, including maternal and pregnancy level factors, birth outcomes, and childhood factors known to associate strongly to study outcomes, such as breastfeeding.

More studies are needed to confirm these results, to examine the relationships of childhood behavior problems with other relevant CVD/T2DM precursors, and to determine the mechanisms explaining the associations reported, including the role of diet and eating behaviors, sleeping patterns, physical activity, smoking in early adolescence, and pathways other than health behaviors, for example those involving neurochemical modifications of the hypothalamus/HPA-axis. Future studies should attempt to clarify the apparent opposite effects of childhood and adulthood depressive symptoms by using designs with longer follow-up periods and repeated assessment of psychopathology and cardiovascular/T2DM risk.

The research presented here has important potential implications. Externalizing problems are identified as a novel childhood risk factor for early development of CVD/T2DM risk, a finding that lends further support to hypotheses of the childhood origins of chronic diseases. These results add to the evidence that physical health is impaired in children with externalizing

problems and suggest that CVD/T2DM risk might need to be monitored in adolescents with a history of externalizing problems. Although not formally tested here, these results also suggest that increased CVD/T2DM risk can develop in these children in the absence of excess adiposity. More research is needed to confirm these findings, to determine the extent to which these associations persist into later ages, and to further investigate the causal mechanism/s that explain these associations.

Figures and Tables

Figure 2. 1: Study di-acyclic graph, DAG 1

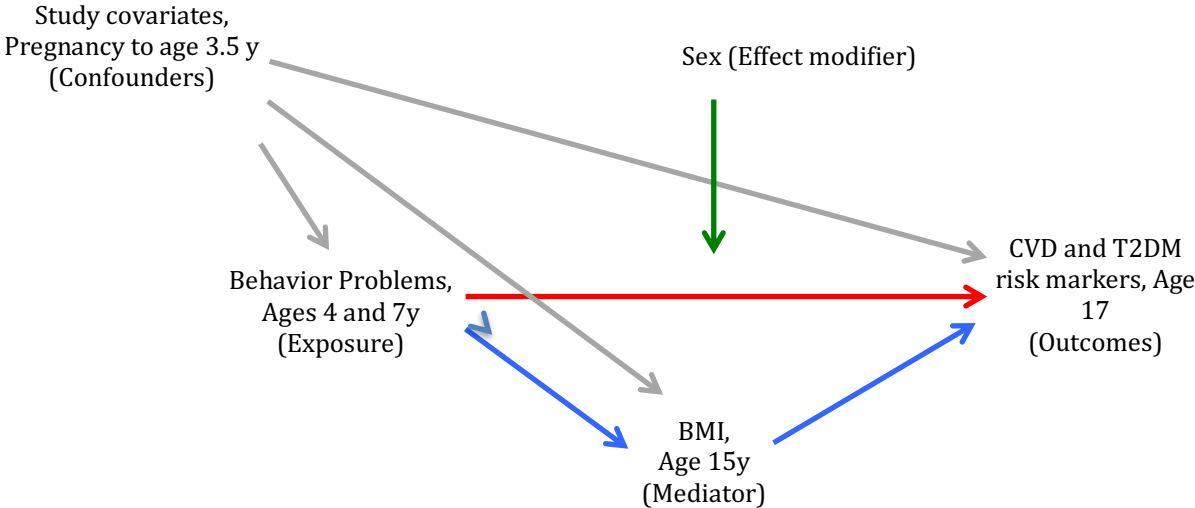


Table 2.1: Distribution of study variables among study participants by BMI status at age 15, and by the study outcomes HOMA-IR, LDL-C, and triglycerides at age 17

	BMI N=7730			HOMA-IR N= 3422			LDL N= 3446			Triglycerides N=3446		
	Below 95 th CDC-Pctl	At or above 95 th CDC-Pctl		Below 85 th Pctl	At or above 85 th Pctl		< 130 mg/dl	≥ 130 mg/dl		< 130 mg/dl	≥ 130 mg/dl	
Total, N (%)	7359 (95.8)	371 (4.8)		2899 (85)	523 (15)		3341 (97)	105 (3)		3068 (89)	378 (11)	
	N (%)		<i>P</i> *	N (%)		<i>P</i> *	N (%)		<i>P</i> *	N (%)		<i>P</i> *
Behavior Problems												
at ages 4 or 7												
Hyperactivity problems												
Never	6523 (88.6)	314 (84.6)	.019	2607 (89.9)	450 (86.1)	.010	2986 (89.4)	93 (88.8)	.863	2763 (90.1)	316 (83.6)	.000
Ever	836 (11.4)	57 (15.4)		292 (10.1)	73 (13.9)		355 (10.6)	12 (11.2)		305 (9.9)	62 (16.4)	

Table 2.1 Cont'd

Conduct

problems

Never	6036 (82.0)	277 (74.7)	.000	2429 (83.8)	423 (80.9)	.104	2783 (83.3)	86 (82)	.721	2579 (84.0)	289 (76.7)	.000
Ever	1323 (18.0)	94 (25.3)		470 (16.2)	100 (19.1)		558 (16.7)	19 (18)		489 (16.0)	88 (23.3)	

Emotional

problems

Never	6654 (90.4)	344 (92.7)	.139	2651 (91.4)	473 (90.5)	.471	3046 (91.2)	100 (95.0)	.163	2790 (90.9)	355 (94.2)	.036
Ever	705 (9.6)	27 (7.3)		248 (8.6)	50 (9.5)		295 (8.8)	5 (5.0)		278 (9.1)	22 (5.8)	

Study covariates

Sex						.182			.000			.850
Male	3761 (51.1)	214 (57.7)	.013	1447 (49.9)	245 (46.8)		1678 (50.2)	29 (27.8)		1519 (49.5)	189 (50.0)	
Female	3598 (48.9)	157 (42.3)		1452 (50.1)	278 (53.2)		1663 (49.8)	76 (72.2)		1549 (50.5)	189 (50.0)	
Race/ethnicity			.396			.574			.252			.045

Table 2.1 Cont'd

Non-white	274 (3.7)	17 (4.6)		112 (3.9)	18 (3.4)		125 (3.7)	6 (5.7)		124 (4.0)	8 (2.0)	
White	7085 (96.3)	354 (95.4)		2787 (96.1)	505 (96.6)		3216 (96.3)	99 (94.3)		2944 (96.0)	370 (98.0)	
Maternal education			.000			.000			.000			.003
Less than high- school	3166 (43)	113 (30.5)		1496 (51.6)	222 (42.4)		1695 (50.7)	35 (33.9)		1568 (51.1)	162 (43.0)	
High School +	4193 (57)	258 (69.5)		1403 (48.4)	301 (57.6)		1646 (49.3)	70 (66.1)		1501 (48.9)	215 (57.0)	
Household income / week			.000			.07			.005			.180
<200	1707 (23.2)	116 (31.3)		539 (18.6)	115 (21.9)		630 (19.0)	28 (27.2)		581 (18.9)	78 (20.5)	
200-399	3755 (51.0)	196 (52.8)		1507 (52.0)	276 (52.8)		1741 (52.0)	55 (52.0)		1589 (51.8)	207 (54.8)	
400+	1897 (25.8)	59 (15.9)		853 (29.4)	132 (25.3)		970 (29.0)	22 (20.8)		898 (29.3)	93 (24.7)	
Family history of diabetes, Yes	313 (4.3)	22 (5.9)	.122	119 (4.1)	23 (4.3)	.857	137 (4.1)	5 (4.8)	.735	131 (4.3)	12 (3.1)	.277
Family history of hypertension, Yes	2432 (33)	125 (37.7)	.797	979 (33.8)	167 (32.0)	.428	1113 (33.3)	42 (39.6)	.177	1026 (33.4)	129 (34.1)	.787

Table 2.1 Cont'd

Family history of heart disease, Yes	922 (12.5)	48 (12.9)	.817	366 (12.6)	71 (13.5)	.578	426(12.7)	13 (12.7)	.993	390 (12.7)	49 (13.0)	.837
Maternal history of diabetes			.030			.067			.323			
Never diabetes	6996 (95.1)	341 (91.9)		2769 (95.5)	491 (93.9)		3185 (95.3)	97 (92.4)		2919 (95.2)	362 (96.0)	.355
Ever diabetes	140 (1.9)	12 (3.2)		49 (1.7)	7 (1.4)		55 (1.7)	2 (2.1)		50 (1.6)	8 (2.0)	
Glycosuria in pregnancy	223 (3.0)	18 (4.9)		82 (2.8)	25 (4.7)		101 (3.0)	6 (5.5)		99 (3.2)	7.4 (2.0)	
Gestational hypertension, Yes	1088 (14.8)	73 (19.7)	.010	440 (15.2)	96 (18.3)	.065	524 (15.7)	16 (15.8)	.982	489 (16.0)	51 (13.6)	.249
Gestational weight gain			.029			.008			.204			.237
Below recommended	966 (13.1)	51 (13.7)		365 (12.6)	73 (13.9)		423 (12.7)	19 (17.9)		388 (12.7)	53 (14.2)	
Within recommended	2260 (30.7)	90 (24.3)		923 (31.8)	131 (25.0)		1027 (30.7)	34 (32.4)		958 (31.2)	102 (27.1)	

Table 2.1 Cont'd

Above recommended	4133 (56.2)	230 (62.0)		1611 (55.6)	319 (61.1)		1891 (56.6)	52 (49.7)		1722 (56.1)	222 (58.7)	
Preterm birth, Yes	376 (5.1)	13 (3.5)	.168	143 (5.0)	31 (6.0)	.343	168 (5.0)	7 (6.7)	.443	156 (5.1)	19 (5.1)	.990
SGA, Yes	676 (9.2)	25 (6.7)	.108	260 (19)	61 (12)	.004	316 (9.5)	7 (6.7)	.387	291 (9.5)	32 (8.5)	.554
LGA, Yes	807 (11.0)	64 (17.3)	.000	337 (12)	69 (13)	.287	402 (12.0)	9 (8.5)	.271	375 (12.2)	36 (9.5)	.123
Breastfeeding			.001			.000			.000			.021
Never	1632 (22.2)	95 (25.6)		549 (19.0)	134 (25.6)		651 (19.5)	37 (35.8)		600 (19.5)	89 (23.5)	
< 3 months	1686 (22.9)	107 (28.8)		636 (22.0)	131 (25.2)		763 (22.8)	10 (9.2)		673 (21.9)	99 (26.3)	
3-5 months	1248 (17.0)	65 (17.5)		502 (17.2)	93 (17.7)		581 (17.4)	18 (16.4)		545 (17.8)	54 (14.2)	
6+ months	2793 (38.0)	104 (28.0)		1212 (41.8)	165 (31.5)		1346 (40.3)	40 (38.6)		1250 (40.8)	136 (36.0)	
BMI at age 15, at or above CDC- 95 th Pctl, Yes	-	-	-	90 (3.1)	81 (15.8)	.000	86 (3.6)	79 (11.8)	.000	109 (4.0)	56 (16.7)	.000
	<hr/> Mean (SD)			<hr/> Mean (SD)			<hr/> Mean (SD)			<hr/> Mean (SD)		
Age, years	15.5 (0.3)	15.5 (0.3)	.235	17.2 (1.1)	16.7 (1.2)	.000	17.1 (1.1)	17.2 (1.0)	.137	17.1 (1.1)	17.2 (1.1)	.060

Table 2.1 Cont'd

Neighborhood stress index	3.75 (3.2)	4.4 (4.1)	.036	3.7 (3.2)	3.9 (3.5)	.279	3.8 (3.2)	3.5 (3.0)	.482	3.7 (3.2)	3.8 (3.6)	.806
Maternal depression score	5.7 (5.2)	5.9 (5.2)	.737	5.7 (4.5)	6.0 (4.9)	.232	5.8 (4.6)	4.7 (4.2)	.014	5.8 (4.6)	5.4 (4.2)	.095
Maternal age at delivery	29.5 (4.4)	28.9 (4.3)	.106	29.4 (4.4)	28.9 (4.5)	.018	29.3 (4.4)	28.8 (3.8)	.174	29.4 (4.4)	28.8 (4.5)	.009
Birthweight (g)	3431 (541)	3546 (530)	.007	3434 (530)	3396 (584)	.129	3430 (530)	3386 (514)	.417	3433 (543)	3390 (496)	.147
Gestational age (weeks)	39.4 (1.8)	39.6 (1.4)	.170	39.5 (1.8)	39.4 (1.9)	.147	39.5 (1.8)	39.4 (1.8)	.782	39.5 (1.8)	39.5 (1.7)	.858

All tables and tests adjusted by IPCW

SGA: Small-for-gestational-age; LGA=Large-for-gestational-age

Table 2. 2: Relative risk of insulin resistance in late adolescence associated with behavior problems in childhood, N=3,422

Behavior problem ¹	HOMA-IR		Model 1 ²	Model 2 ³	Model 3 ⁴	Model 4 ⁵	<i>p</i> ⁶
	< 85 th	≥ 85 th					
	Percentile	Percentile					
	N		RR (95% CI)				
Hyperactivity problems							0.274
Never	2607	450	1.00	1.00	1.00	1.00	
Ever	292	73	1.32 (1.05 - 1.66)	1.27 (1.01 - 1.59)	1.28 (1.01 - 1.61)	1.23 (0.98 - 1.54)	
Conduct problems							0.981
Never	2430	423	1.00	1.00	1.00	1.00	
Ever	469	100	1.17 (0.96 - 1.44)	1.12 (0.91 - 1.38)	1.13 (0.92 - 1.39)	1.08 (0.88 - 1.32)	
Emotional problems							0.349
Never	2651	473	1.00	1.00	1.00	1.00	
Ever	248	50	1.08 (0.82 - 1.42)	1.04(0.78 - 1.37)	1.05 (0.79 - 1.39)	1.11 (0.85 - 1.47)	

¹ Behavior problems (hyperactivity, conduct, and emotional problems) were all modeled separately

² Model 1 is adjusted for: Age, sex, race/ethnicity

³ Model 2 is adjusted as model 1 plus: Maternal education, Household income, maternal age at delivery, and maternal depression

⁴ Model 3 is adjusted as model 2 plus maternal weight-gain during pregnancy, gestational hypertension, child's birth weight, and breastfeeding

⁵ Model 4 is adjusted as model 3 plus BMI at age 15 ≥ CDC-95th percentile

⁶ p-value for the behavior problem*sex interaction term added to model 3

²⁻⁶ All models are weighted by IPCW.

Table 2. 3: Relative risk of high LDL-Cholesterol levels in late adolescence associated with behavior problems in childhood, N=3,446

Behavior problem ¹	LDL-Cholesterol		Model 1 ²	Model 2 ³	Model 3 ⁴	Model 4 ⁵	<i>p</i> ⁶
	< 130	≥ 130					
	mg/dl	mg/dl					
	N	RR (95% CI)					
Hyperactivity problems							0.692
Never	2986	93	1.00	1.00	1.00	1.00	
Ever	355	12	1.30 (0.69 – 2.44)	1.24 (0.66 – 2.33)	1.22 (0.66 – 2.25)	1.12 (0.62 – 2.04)	
Conduct problems							0.572
Never	2783	86	1.00	1.00	1.00	1.00	
Ever	558	19	1.16 (0.71 - 1.90)	1.16 (0.70 - 1.94)	1.09 (0.65 - 1.85)	1.02 (0.61 - 1.68)	
Emotional problems							0.889
Never	3046	100	1.00	1.00	1.00	1.00	
Ever	295	5	0.54 (0.22 - 1.35)	0.56 (0.23 - 1.39)	0.61 (0.25 - 1.51)	0.62 (0.25- 1.57)	

¹ Behavior problems (hyperactivity, conduct, and emotional problems) were all modeled separately

² Model 1 is adjusted for: age, sex, and race/ethnicity

³ Model 2 is adjusted as model 1 plus: Maternal education, household income, maternal age at delivery, and family history of heart disease

⁴ Model 3 is adjusted as model 2 plus: maternal weight gain during pregnancy, and breastfeeding

⁵ Model 4 is adjusted as model 3 plus BMI at age 15 ≥ CDC-95th percentile

⁶ p-value for the behavior problem*Sex interaction term added to model 3

²⁻⁶ All models are weighted by IPCW

Table 2. 4: Relative risk of high triglyceridemia in late adolescence associated with behavior problems in childhood, N=3,446

Behavior problem ¹	Triglycerides		Model 1 ²	Model 2 ³	Model 3 ⁴	Model 4 ⁵	<i>p</i> ⁶
	< 130 mg/dl	≥ 130 mg/dl					
	N		RR (95% CI)				
Hyperactivity problems							0.509
Never	2764	315	1.00	1.00	1.00	1.00	
Ever	305	62	1.68 (1.30 - 2.18)	1.65 (1.27 - 2.14)	1.61 (1.24 - 2.09)	1.50 (1.16 - 1.95)	
Conduct problems							0.254
Never	2580	289	1.00	1.00	1.00	1.00	
Ever	489	88	1.53 (1.22 - 1.92)	1.52 (1.21- 1.92)	1.51 (1.20 - 1.90)	1.42 (1.13 - 1.79)	
Emotional problems							0.571
Never	2791	355	1.00	1.00	1.00	1.00	
Ever	278	22	0.65 (0.43 - 0.99)	0.65 (0.43 - 0.99)	0.66 (0.42 - 0.99)	0.67 (0.44 - 1.02)	

¹ Behavior problems (hyperactivity, conduct, and emotional problems) were all modeled separately

² Model 1 is adjusted for: Age, sex, and race/ethnicity

³ Model 2 is adjusted as model 1 plus: maternal education, maternal age at delivery, and maternal depression

⁴ Model 3 is adjusted as model 2 plus: child's birth weight, and breastfeeding

⁵ Model 4 is adjusted as model 3 plus BMI at age 15 ≥ CDC-95th percentile

⁶ p-value for the behavior problem*Sex interaction term added to model 3

²⁻⁶ All models are weighted by IPCW

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Appendix for Chapter 2

Figure A.2. 1: Study sample flow chart

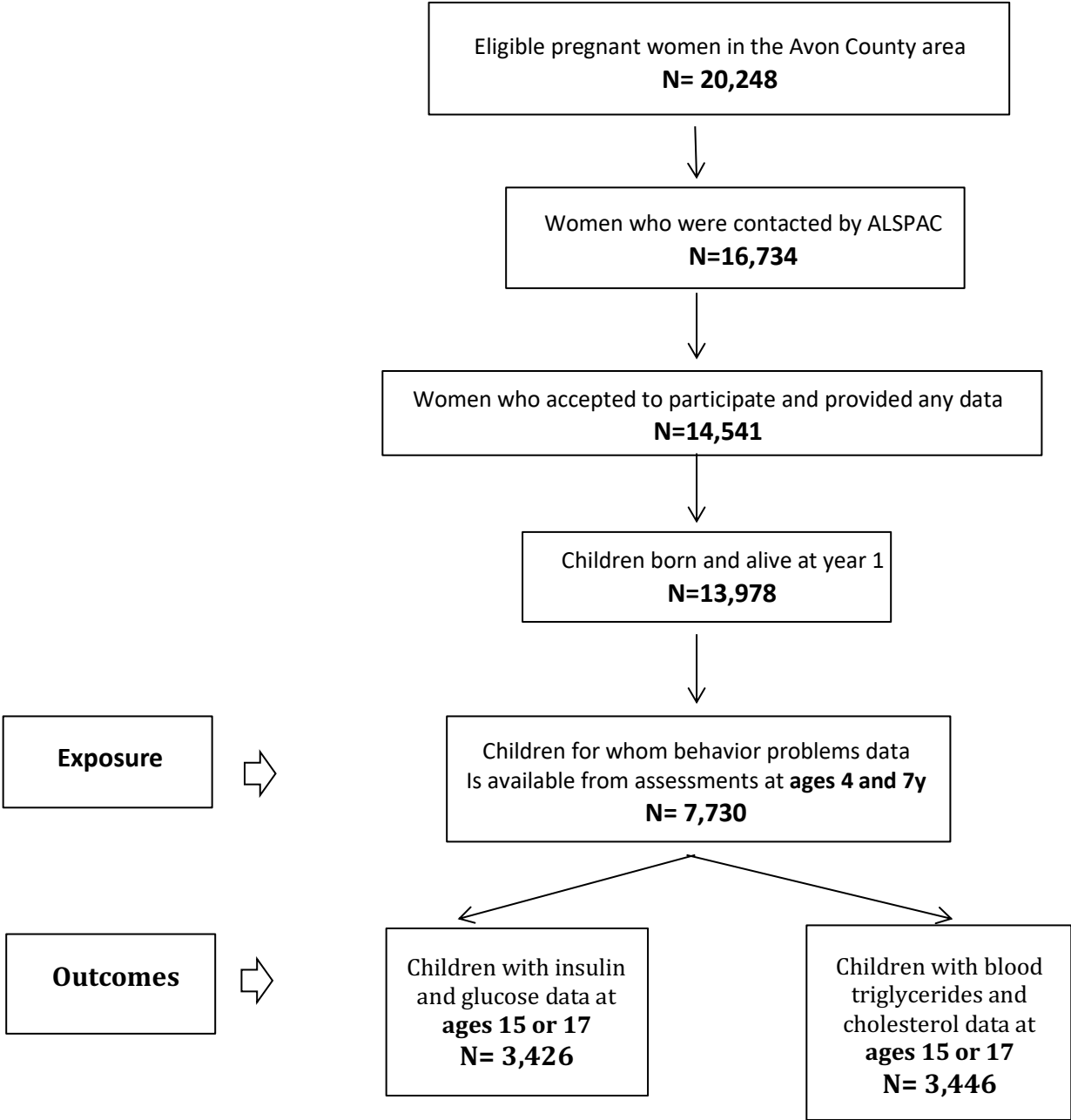


Figure A.2. 2: Timing of assessment of study variables

Pregnancy	Birth	Age 1y 9mos	Age 2y 9mos	Age 4y	Age 7y	Age 15y	Age 17y
Covariates				Exposure: <i>Behavior problems</i>		Outcomes: <i>CVD and T2DM risk markers</i>	
-Maternal education	-Gestational age at birth	-NHBD ¹ stress	-Household income	-Behavior problems	-Behavior problems	-IR ²	-IR
-Pre-pregnancy BMI	-LGA ⁵ , SGA ⁶	-Maternal depression				-TG ³ , LDL-C ⁴	-TG ³ , LDL-C ⁴
-Pregnancy weight gain	-Maternal age at delivery					-BMI (mediator)	
-Maternal history of diabetes							
-Family history of CVD ⁷ and T2DM ⁸							
-Gestational diabetes							
-Gestational hypertension							

¹ NHBD: Neighborhood

² IR: Insulin Resistance

Figure A.2.2 Cont'd

³ TG: Triglycerides

⁴ LDL-C: Low-density lipoprotein Cholesterol

⁵ LGA: Large-for-gestational-age

⁶ SGA: Small-for-gestational-age

⁷ CVD: Cardiovascular disease

⁸ T2DM: Type-2 diabetes mellitus

Table A.2. 1: Comparison of the prevalence of behavior problems at baseline between the original sample and the sample retained through follow-up

Behavior problems	Frequency		p-value
	Baseline sample n= 7330	Retained sample n= 3446	
Age 4 years			
Externalizing problems			
Hyperactivity	13.7	12.7	0.18
Conduct problems	12.3	11.5	0.23
Internalizing problems			
Emotional problems	4.3	4.0	0.46
Peer problems	10.2	10.0	0.75
Age 7 years			
Externalizing problems			
Hyperactivity	10.7	9.4	0.03
Conduct problems	10.3	8.7	0.01
Internalizing problems			
Emotional problems	6.4	5.9	0.27
Peer problems	6.7	6.1	0.22

Table A.2. 2: Comparison of the prevalence of study covariates between the original sample and the sample retained through follow-up

Variables	% Missing in baseline sample	Frequency, mean, or median		P-value
		Baseline sample	Retained sample	
		N= 7330	N= 3446	
Sex, Female	0	51.4	49.7	.084
Ethnicity, Non-white	0.34	3.8	3.9	.830
Household weekly Income	13.7			
< 100		6.9	4.9	<.001
100-199		16.0	13.6	
200-299		29.0	27.9	
300-399		22.4	24.4	
>400		25.8	29.2	
Mom's education,	5.7			
Above "O-level"		56.7	48.9	<.001
Neighborhood stress score, median	6.0	3.0	3.0	.736
Mom's depression score, median	4.0	5.0	5.0	.161
Mom's anxiety score, median	4.9	3.0	3.0	.225
Pre-pregnancy weight, mean	8.5	60.6	60.6	.842
Pregnancy diabetes	0.4	3.5	3.5	.950
Pregnancy hypertension	2.4	14.9	15.5	.397
Family history of diabetes	2.0	4.3	4.3	.967
Family history of heart disease	2.0	12.6	13.0	.526

Table A.2.3: Co-occurrence of behavior problems, by age at assessment

Age 4 years

Hyperactivity problems		Conduct problems		Emotional problems	
N= 602		N=953		N=331	
	%		%		%
Conduct problems	43	Hyperactivity problems	27	Hyperactivity problems	20
Emotional problems	11	Emotional problems	10	Conduct problems	30

Age 7 years

Hyperactivity problems		Conduct problems		Emotional problems	
N=487		N=793		N=495	
	%		%		%
Conduct problems	42	Hyperactivity problems	26	Hyperactivity problems	20
Emotional problems	21	Emotional problems	19	Conduct problems	30

Chapter 3:

Childhood Externalizing Problems and Elevated Triglyceride Levels in Adolescence: Causal Explanations

Abstract

Common childhood externalizing behaviors such as hyperactivity and conduct problems are risk factors for obesity throughout the life course. Whether these behavioral diagnoses increase cardiometabolic risk in early life independently of their effect on body adiposity is currently unknown. We investigated the prospective association of childhood (ages 4 and 7 years) hyperactivity and conduct problems with clinically high levels of triglycerides in adolescence in a large birth-cohort study, the Avon Longitudinal Study of Parents and Children (ALSPAC). Using causal mediation methods, we tested for indirect effects (NIE) mediated by diet, sleep, physical activity, smoking, alcohol use and body mass index, as well as direct or no mediated- effects (NDE). Results: In both fully adjusted logistic-regression models, hyperactivity problems (OR= 1.74, 95% CI = 1.29-2.37) and conduct problems (OR= 1.60, 95% CI = 1.23-2.09) were associated with increased triglycerides. Mediation analysis showed that the association of hyperactivity (NDE OR= 1.48, 95% (CI=1.12 -1.89), NIE OR= 1.08, (95% CI=0.98-1.14) and conduct problems (NDE OR= 1.40, (95% CI=1.10 -1.72), NIE OR= 1.07, (95% CI=0.98-1.14)) with triglycerides were only partially mediated. Body mass index and lifestyle health behaviors jointly mediated 19.6 % and 19.3% of the total effects of hyperactivity and conduct problems on triglycerides, respectively. Conclusions: Childhood hyperactivity and conduct problems are associated with high levels of triglycerides in adolescence. Hyperactivity and conduct problems appear to influence triglycerides mostly independently of body mass index, and lifestyle health behaviors.

Introduction

Attention-deficit /hyperactivity disorder, ADHD, is the most common behavioral diagnosis among children in the US, with a prevalence estimated by the 2016 National Survey of Children's Health (NSCH) of 8.9 % among children aged 3-17 years. Among children with ADHD, 51 % had additional behavioral or conduct problems¹. Determining the ways and extent to which childhood ADHD and conduct problems influence health through the life course is important, in particular, given that other more extensively studied mental health problems, such as mood disorders and anxiety, are now considered important contributors to the development of cardiovascular diseases²⁻⁵.

Although less investigated than mood disorders and anxiety problems, there is evidence of associations between ADHD and conduct problems with increased body adiposity in young and mid-adulthood⁶⁻⁹, which is itself associated with higher risk of cardiovascular disease. There is also some evidence that these associations may extend to CVD risk factors other than adiposity, and CVD itself.

In a prospective, population-based study, distress proneness at age 7 was a strong predictor of type-2 diabetes in mid-adulthood¹⁰. In another large cohort study¹¹, hyperactivity at age 7 predicted increased carotid intima-media thickness in adulthood among women, and in the same cohort, high self-control (a measure of low externalizing problems) predicted absence of coronary-artery calcification¹². In yet another prospective study¹³ with long follow-up, conduct disorder at age 13 was predictive of death from CVD before age 65. And, in a cross-sectional examination of young US adults (NHANES), having 3+ DSM-IV symptoms of hyperactivity/impulsivity (retrospectively reported) was associated with CDC-defined Stage II hypertension¹⁴.

Indeed, my own prior research in the same sample as the present study, has shown what might be the first evidence to-date in a prospective cohort of a positive association of childhood hyperactivity and conduct problems with adolescent levels of triglycerides, a biological marker causally related to heart disease. In that analysis, children with hyperactivity or conduct problems were almost twice as likely to have clinically significant high levels of triglycerides at age 17. The associations of hyperactivity and conduct problems with triglycerides persisted after adjusting these behavior problems for each other and after adjusting for the children's depressive symptoms, and a wide-range of family socio-demographic characteristics, history of CVD risk, maternal pre- and pregnancy factors, pregnancy outcomes, maternal mental health, and breastfeeding. These findings of a prospective association of hyperactivity and conduct problems with triglycerides were further strengthened by the observation that triglyceride levels did not vary between children with- and without hyperactivity or conduct problems at study baseline.

A question that remains unclear in this literature is what may mediate the relationship between externalizing problems and CVD risk. While some of the literature discusses the neuroendocrine system, with dysregulation of the HPA-axis, as a potential pathway¹⁵, the most prominent hypothesis posits that these effects are largely mediated by mechanisms involving health behaviors, specifically, behaviors associated with increased body adiposity --poor diet, poor sleeping habits, sedentary lifestyle-- and by stress-coping, and sensation-seeking behaviors such as cigarette smoking, and alcohol use. Externalizing psychopathology is associated with impulsiveness, low-inhibitory control, and low self-regulation. These symptoms have been shown to associate with a myriad of negative health-behaviors, including overeating, and binge eating¹⁶, consumption of unhealthy diets with high content of sugar, low ratios of unsaturated-to-saturated fats, low in fiber content, and high intake of sugar-sweetened beverages¹⁷. Adolescents with

hyperactivity/inattention and conduct problems were found to be less physically active than peers¹⁸. Sleep disruption and shortened sleep are very common among children with ADHD^{19,20} and/or conduct problems²¹, and compared with peers, these children tend to start drinking alcohol and smoking earlier, and to consume more alcohol and smoke more than their peers²². All of these behaviors have, in turn, been shown to associate with increased CVD risk.

Unveiling what these mechanisms might be is important for three reasons. First, it could strengthen the case that these relationships are indeed causal. Second, it could help us better understand the ways by which psychopathology is biologically embedded to increase CVD risk. Third, it could help inform the design of interventions to reduce cardiometabolic risk in children with externalizing problems. And fourth, determining the extent to which externalizing symptoms increase CVD risk independently of adiposity has important implications for prevention, as it would suggest that BMI might not be a sufficiently sensitive measure to screen for CVD risk in children with hyperactivity or conduct problems.

In the present study, and extending my prior research, I examined the mechanisms that underlie the prospective association of childhood externalizing problems with high levels of triglycerides in adolescence. Using data from a large population-based study, I assessed whether childhood hyperactivity and conduct problems had direct effects on triglyceride levels at age 17. Direct effects were defined as the effects that did not work by pathways involving health behaviors or BMI, all assessed throughout the follow-up period. In addition, I also estimated the proportion of the total causal effects of hyperactivity and conduct disorder that was explained by those pathways, or indirect effects.

I hypothesized that hyperactivity and conduct problems influence triglycerides mostly by indirect, or mediated pathways. I further hypothesized that childhood BMI and health behaviors

are more important mediators, that is, that together they contribute more to the overall mediated effect, than adolescence BMI (See Fig. 3.1).

Methods

Setting and participants

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a large, trans-generational birth-cohort study established in South West of England (Avon County of the Bristol area). The study, which drew from the general population, recruited pregnant women with expected dates of delivery between April 1, 1990, and December 31, 1992. ALSPAC's core sample is made up of the 13,978 children that remained alive by year 1. The study design has been previously described in detail^{23,24}. Briefly, throughout follow-up, the study assessed children by means of questionnaires completed by the main caretaker, child-completed questionnaires, and clinical assessments of physical health, starting at age 7. This analysis is based on the subsample of children for whom complete data on behavior problems (exposure of interest) was available from assessments at ages 4 and 7 years (n=7730). This study follows this subsample up until clinic assessments at age 17 years. Of the 7730 participants included at baseline, n=3446 (45%) participants attended this clinic and provided measures for the study outcome. The degree of study attrition observed is similar to that reported in most other large, population-based, cohort studies. Compared with retained ones, lost to follow-up participants were more likely to have been classified as having externalizing problems at baseline, came from households with lower income, and had mothers with lower educational attainment (Appendix tables A.2.1 and A.2.2).

Censoring weights

Inverse probability of censoring weights (IPCW) was used to account for possible biases due to study attrition over the 10-year follow-up (55%). Weights were estimated as follows: I created a binary variable to indicate censoring (0=Outcome information available, 1=No outcome

information available). I fitted logistic regression models to estimate the unconditional and conditional probabilities of remaining uncensored ($C=0$) using behavior problem variables, conduct and hyperactivity problems, and study covariates as predictors of censoring status. Stabilized Censoring Weights (SCW) were estimated as: $= P(C=0) / P(C=0 | A, Cov)$, where “A” represents variables reflecting the status on conduct and hyperactivity problems at each assessment point, ages 4 and 7, and “Cov” represents study covariates. The mean SCW was in the 0.999 - 1.000 range and the range of weights was 0.61-1.51. These weights were applied to all tests for statistical differences of bivariate associations and regression models for the study outcome.

Study Measures

Behavior Problems

Behavior problems in study participants were assessed using the parent version of the Strengths and Difficulties Questionnaire (S&D) completed by the mothers or main caregivers at participants’ age 4 and 7-year follow-up.

The S&D is a widely used tool for the assessment of common behavioral psychopathology in children of school age in large, non-clinical samples. It is composed of 25 items covering 4 problem behaviors (emotional, hyperactivity, conduct, and peer problems) and one positive behavior (pro-social behaviors). Parents rate their child with respect to each of the 25 behaviors over the prior 6 months. Scoring produces a total score that is considered a valid measure of the child’s overall psychological wellness as well as 5 subscale scores: emotional problems, hyperactivity problems, conduct problems, peer problems and pro-social score. My analyses used the hyperactivity and conduct problems scores obtained at the 4 years and 7 years old assessments. S&D scores correlate well with interview measures, differentiate clinical from non-clinical

samples, and correlate with clinical diagnoses of behavioral psychopathology. The reliability of the S&D scale was found to be satisfactory in a study using a large, nationally representative sample of British children aged 5-15 years (N=10,438) with mean Cronbach's alpha across subscales 0.73, and mean, across subscales 4-6 months test-retest reliability equal to 0.62²⁵.

Scoring of the S&D questionnaire: Items in the scale are rated 0=Not true, 1=Somewhat true, and 2=Certainly true, with five items reverse-coded. Each of the subscales is scored separately by adding up the 5 items within them (Scores range= 0-10). Cut-off points for each subscale defining the categories "Close to average" (bottom 80%), "Slightly raised" (10%), "High", (5%) and "Very high" (5%) have been estimated based on a large, non-clinical sample of British school-aged children. In this study, I created two binary variables: 1) Ever hyperactivity problems (Ever HP), and 2) Ever conduct problems (Ever CP), each reflecting whether the participant was ever reported (at either age 4 or age 7 assessments) to be in the "High" or "Very High" categories as defined above.

Triglyceride levels

Fasting blood samples were obtained from participants at the age 15 and age 17 clinics, with some participants attending just one of the clinics. In this analysis I used age 17 clinic measures when available (73 % of participants) and age 15 measures otherwise, and multivariate analyses adjusted for age at assessment of triglycerides. Participants were instructed to fast overnight if they attended the clinic in the morning or to fast for at least 6 hours (they missed lunch) if attending in the afternoon. Blood samples were processed soon after collection, plasma was separated and immediately frozen at -80°C , without freeze-thaw cycles, until assays were conducted three to nine months later. Triglycerides levels were determined using a modified

version of the standard Lipid Research Clinics Protocol that employs enzymatic reagents. For these analyses, triglyceride levels were classified as “High” (≥ 130 mg/dl) versus “Not high” (< 130 mg/dl), as recommended by the National Health of Blood and Lung Institute Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, 2011²⁶, for children ages 10-19 years.

Study covariates

Information on all study covariates was obtained during the period between recruitment into the study, at pregnancy, and the study participant’s first assessment of behavior problems (study exposure) at age 4 years. Information was obtained via questionnaires, completed by the mother or main caretaker, or was extracted from antenatal medical records of mothers if consent was attained. Information obtained during pregnancy included: participant’s ethnicity (White/Caucasian or other), maternal highest educational attainment (Below O-level -equivalent to less than completed secondary education-, O-level, A-level -some certification beyond secondary education), number of previous pregnancies, whether the mother’s biological parents had any of diabetes (Yes, No), hypertension (Yes, No), and heart disease (Yes, No). Information collected between birth and participants’ age of 4 years included: breastfeeding (never, < 3 months, 3-5 months, 6+ months); maternal depression (Edinburgh Post Natal Depression Scale, total score was used); household weekly income (less than £100, £100-199, £200-299, £300-399 and £400+); and neighborhood stress index (range 0-22, estimated by 11 questions about housing and neighborhood conditions). Information extracted from antenatal medical records included: maternal age at delivery, birth weight, gestational age at delivery, maternal history of diabetes (never, ever before pregnancy, only during pregnancy), gestational hypertension (Yes, No), and

weight gain through pregnancy (less than recommended, as recommended, or above recommended, according to Institute of Medicine). These covariates were chosen based on prior literature indicating that they were or were possibly associated with childhood behavior problems and with cardiometabolic risk. Additional demographic and stressor variables available in the study, such as father's and mother's social class, were initially included but were ultimately not used because they were highly correlated with other covariates and did not appear to account for any significant residual confounding once other variables were already adjusted for.

Study mediators

1. Health Behavior variables

Sleep at age 10 years

I estimated average daily number of sleep hours based on mother's answers to a mailed questionnaire. Mothers answered to questions including "What time (to the nearest minute) does your child normally go to bed in the evening" and a similar question for usual wake-up time in the morning. Sleep hours on weekdays and weekends were queried separately. Answers were used to compute weekday and weekend average number of sleep hours. A variable indicating mean hours of sleep per day was derived after assigning proper weights to week and weekend average sleep hours.

Dietary variables at age 13 years

Dietary intake was assessed at age 13 by the administration of 3-day food diaries^{27,28} mailed to participants prior to their clinic visits. Participants were asked to record, with assistance from

parents or caretakers if needed, all foods and beverages consumed over two week days and one weekend day. At the clinic, participants interviewed with nutritionists to verify completeness of diaries, clarify notions of portion sizes, and strengthen inconsistencies in the reporting^{27,28}. Children who did not provide dietary diaries (fewer than 10%) completed twenty-four-hour recalls²⁷. The software DIDO (Diet In, Data Out), developed by the MRC Human Nutrition Research Unit (Cambridge, UK)²⁸, was used for coding and weighting of foods data. Mean daily nutrient intakes were estimated using the nutrient analysis software BRIGADE.

Dietary variables used in this analysis include total energy intake (kilocalories per day) (E), percent of total energy from fat (% E from fat), percent of total energy from carbohydrates (CHO) (% E from CHO), and number of sugar-sweetened beverage (SSB) servings per day. As done in prior ALSPAC studies^{28,29} I defined SSB as full-sugar fruit squashes, cordials, and fizzy drinks (i.e. soda) with added sugar. Squashes and cordials were recorded as full-volume (syrup plus added water), or as concentrate (without water). It was assumed that 140 g of water were added to 40 g of concentrate for drinking. A one serving of SSB was defined as 180 grams of beverage (1 cup), that is, 180 g of full-volume beverage or 40 g of concentrate.

Dietary reporting error

Error in self-reporting of food intake is common in epidemiological studies and has been described before³⁰. Inverse or null associations between reported energy intake and BMI are often observed³⁰. Although completely accounting for the bias caused by this error is unfeasible, methods have been developed that allow for the accounting of some of that bias.

The method developed by *Huang et al.*³¹ was applied to determine which participants had provided dietary intakes that were plausible given their age, sex, height, weight, and measured level of physical activity. For each participant, an R-value was estimated as:

$R = \text{Reported energy intake (rEI)} / \text{Estimated energy expenditure (EEE)}$, where $EEE = \text{Total Energy Expenditure (TEE)} + \text{Constant for energy deposition growth}$, and $TEE = \text{BEE (Basal Energy Expenditure)} \times \text{Physical activity level (PAL)}$. Age-, sex-, height, and weight-specific BEE values were estimated applying formulas published by the DRI³² using participant's own data. PAL levels were assigned based on DRI guidelines³², using the participant's estimates of MVPA (Minutes of moderate-to-vigorous physical activity per day) from accelerometer data.

Using formulas for error propagation, age- and sex- specific 1 SD cutoffs for the R value were estimated as: $1 \text{ SD} = \sqrt{CV_{rEI}^2/d + CV_{pER}^2 + CV_{mTEE}^2}$, and CV_{rEI}^2 , where CV_{rEI}^2 is the sample specific coefficient of variation in reported energy intake, d is the number of days of dietary reporting, CV_{pER}^2 is coefficient of variation in the estimation of energy requirements by DRI formulas, and CV_{mTEE}^2 is the coefficient of variation in the measurement of TEE by doubly-labeled water protocols, from elsewhere in the literature. I used sex-and age-specific values for CV_{rEI}^2 , and CV_{pER}^2 previously estimated for this ALSPAC sample and reported by Noel et al³³.

Participants with R -values within cutoffs (42 % of the sample) were considered “plausible” dietary reporters.

Physical Activity at age 13 years

Physical activity was objectively measured by using MTI Actigraph AM 7164 2.2 accelerometers^{34,35}. Children were asked to wear the accelerometer for 7 days. Data was considered

valid if the accelerometer was worn for at least 3 days, 10 hours per day³⁴. The measure used in this analysis was average counts per minute (CPM) of overall activity per day.

Alcohol intake at age 13 years

Alcohol intake was assessed as part of dietary assessment. Participants recorded any intake of alcohol and the amount of alcohol was averaged over the days of diet assessment to obtain a measure of mean alcohol intake (grams/day). A binary variable was created to classify children as “High alcohol drinkers” or “Not high alcohol drinkers” using the 5 grams of alcohol per day cut-off point.

Cigarette smoking at age 15 years

Participants completed a questionnaire about cigarette smoking at the 15-year clinic. Participants reported whether they were currently smokers, and if so, the frequency of smoking. In this study I classified participants as being smokers (Yes, No) if they reported smoking a cigarette a-day for the past 30 days.

2. Body Mass Index, at ages 8 and 15 years

Height and weight were assessed at the 8 and 15-year clinics with participants wearing only light clothes and no shoes. Using Tanita scales weight was recorded to the nearest 0.1 kg. Height was assessed with Harpende stadiometer and recorded to the nearest 0.1 cm³⁶. BMI was calculated as weight (kg)/ height (cm)². I created a variable to reflect BMI at age 8, another variable to reflect BMI change from age 8 to age 15, and a third variable to reflect whether participants qualified or not as obese at age 15 based on the CDC-published 95th percentile point of BMI for

age (in months) and sex.

Missing covariate information

The proportion of missing covariate values was, as one would expect, lower for covariates assessed during pregnancy and infancy than for covariates during follow up, in late childhood and adolescence. The proportion of missing values in variables considered confounders was typically below 5% and was the greatest for family income at 13%. Among variables considered mediators, all assessed during follow-up, the proportion of missing values was in general below 12 % and was the greatest for one variable related to sleep at 16%. Missing covariate information was assumed to be at random and was imputed using *IVEware* software generating five complete databases. All study variables were used to inform imputation. Analyses were conducted separately in each of these five databases and the inferences resulting from those separate analyses were combined to produce summary effect measures and covariance matrixes with SAS *proc mianalize*.

Analytical approach

I examined the characteristics of participants by looking at the distribution of study variables and assessing bivariate associations by means of statistical tests for the difference of means (t-test), medians (Mann-Whitney test) or frequencies (Chi-Square), as appropriate for each comparison. We used multiple logistic regression to assess the main associations --the relationship of hyperactivity and conduct problems with triglycerides. To be able to interpret odds ratios as estimates of relative risk, I invoked the rare disease assumption, even though the prevalence of the

study outcome (high triglyceride levels) was 11.6 %, just slightly above the arbitrary cut-off point of 10 % set for the definition of rare outcome. When I used other regression approaches that readily provide measures of relative risk for non-rare outcomes (i.e. Log-Binomial Regression), models systematically ran into convergence problems after only a few covariates had been added in. A comparison of odds ratios and risk ratios from small models for which both statistical approaches could be applied without running into convergence issues, showed that, odds ratios overestimated risks. This overestimation did not exceed a factor of 1.1, which was considered acceptable. Logistic regression models were first adjusted for age at which triglycerides were assessed (17 or 15 years), sex, and race. Models were then further adjusted for additional demographics, maternal characteristics, family history of cardiometabolic disorders, pregnancy and gestation-level covariates, birth outcomes, and breastfeeding.

Mediation analysis

I conducted mediation analysis to investigate mechanistic pathways linking hyperactivity and conduct problems with triglycerides. Following the causal inference literature^{37,38} the counterfactual approach was used to assess the role of several health behaviors and BMI as potential mediators of the main effect. These mediators were identified in the literature as being both associated with pre-existing conduct and hyperactivity problems, as well as predictors of elevated triglyceride levels. Through mediation analysis I sought to estimate how much of the total effects of hyperactivity and conduct problems on triglycerides operated through these specific mediators (indirect effects) and how much operated not through the mediators (direct effects).

The counterfactual framework has advanced the traditional approach for mediation analysis, developed by Baron & Kenny, in at least two important ways: 1) It has explicitly articulated and clarified the non-confounding assumptions that are needed for estimates of direct and indirect effects to have causal interpretation. Importantly, some of these assumptions are not exclusive to the counterfactual approach. Though seldom acknowledged, they are also required for causal inference within the traditional approach. 2) Unlike the traditional approach, the counterfactual approach allows for total effect decomposition into direct and indirect effects that have causal interpretation even in the presence of interactions and non-linearities.

The counterfactual approach provides estimates referred to as “natural effects” (direct and indirect effects). In the estimation of natural effects the mediator is set at the values that it naturally takes under the different levels of the exposure in the sample where the main effect has been identified, therefore natural effects better preserve the exposure-outcome relationship³⁹ and have an easier, and more intuitive causal interpretation. The counterfactual framework is, for these reasons, a more appealing approach in ideological mediation analyses that aim primarily at assessing pathways, or determining the relative importance of pathways to the total effect. The traditional approach, on the other hand, produces effects referred to as “controlled effects”, and in its estimation, the mediator is assigned to a fixed level in the whole population. Controlled effects are therefore more useful in evaluating the effect of interventions on the mediator.

When more than one mediator is of interest, as in this analysis, the usual approach of assessing one mediator at a time may not be appropriate. If, for instance, one mediator affects another mediator, the pathways from exposure to outcome through these mediators would at least partially overlap, and that overlapping section of the pathways would be counted twice if the mediators were assessed one at a time. Consequently, the sum of their proportions mediated would

total more than 100%, even if both mediators acted in the same direction. When the temporal order of the mediators is known, it is possible to assess the mediators sequentially, that is, to progressively add mediators to the model from first to last. When we add an additional mediator to a model, we determine 1) the joint mediated effect, and 2) the additional contribution of the last added mediator to the effect of mediators already in the model.

Strategy for the assessment of mediation with multiple mediators

I assessed mediation applying a sequential approach whereby mediators were added to the outcome model (which already included the specific explanatory behavior problem variables and confounding variables) in the order the mediators were assessed (See Fig. 3.2). In the first step I added BMI at 8 years. The estimated NDE at this step indicated the effect of hyperactivity or conduct problems on triglycerides through all pathways except the pathway that operates through BMI at age 8, while the estimated NIE indicated the effect mediated by BMI at age 8. In the next step, I added to the model all health behaviors assessed at ages 10-13 years: % of energy from fat, % of energy from carbohydrates, unsaturated/ saturated fats ratio, SSB, sleep, physical activity, and alcohol intake. The NDE in this step indicated the effect of pathways not through BMI at age 8 or health behaviors at ages 10-13 years, and the NIE indicated the effect through these mediators jointly. In the third step I added two variables, a variable indicating BMI change from ages 8 to 15 years, and a variable indicating whether the participant was obese at age 15, and in the last step I added smoking at age 15, with the corresponding NDE and NIE at these steps being interpreted following the same logic as above.

I tested for exposure-mediator interactions, separately for each mediator. Exposure-mediator interaction terms were included in the models if they caused a change in the estimated NDE and NIE of 10% or more.

Applying the counterfactual approach to assessment of mediation

Definition of Natural Effects

Let A denote the subject's exposure, let Y denote the subject's outcome, let M denote the subject's value of the mediator, and let C denote the values of a vector of confounding variables that may affect, A, M, and/or Y. The **natural direct effect, NDE**, for a binary outcome and on the odds ratio scale, expresses how much the odds ratio would change, on average, if the exposure were set, possibly contrary to fact, at a higher level versus the exposure set to a lower level, and for each individual the mediator were set at the level it would have taken, for that individual, if the exposure was in the lower level.

In formal terms the NDE is defined as:

$$OR_{a,a^*|c}^{NDE}(a^*) = \frac{P(Y_{aM_{a^*}}=1|c)/\{1-P(Y_{aM_{a^*}}=1|c)\}}{P(Y_{a^*M_{a^*}}=1|c)/\{1-P(Y_{a^*M_{a^*}}=1|c)\}}$$

Where $Y_{aM_{a^*}}$ is the subject's value for the outcome Y if the exposure A were set, possibly contrary to fact, to a higher value =a, and the mediator M were set to what it would have been if A had a lower value=a*. $Y_{a^*M_{a^*}}$ is the subject's value for the outcome Y if the exposure A were set, possibly contrary to fact, to a lower value =a* and the mediator M were set to what it would have been if A had a lower value=a*.

The **natural indirect effect, NIE**, expresses how much the odds ratio would change on average if the exposure were fixed, possibly contrary to fact, at a higher level $A=a$, and for each individual the mediator M were changed from the level it would take if the exposure was in the lower level $A=a^*$ to the level it would take if the exposure was in the higher level $A=a$.

In formal terms the NIE is defined as

$$OR_{a,a^*|c}^{NIE}(a) = \frac{P(Y_{aM_a}=1|c)/\{1-P(Y_{aM_a}=1|c)\}}{P(Y_{aM_{a^*}}=1|c)/\{1-P(Y_{aM_{a^*}}=1|c)\}}$$

Where Y_{aM_a} is the subject's value for the outcome Y if the exposure A were set, possibly contrary to fact, to a higher value $=a$, and the mediator M were set to what it would be if A had a higher value $=a$. $Y_{aM_{a^*}}$ is the subject's value for the outcome Y if the exposure A were set, possibly contrary to fact, to a higher value $=a$, and the mediator M were set to what it would be if A had a lower value $=a^*$.

As clarified by the causal inference literature, these effects are identifiable under the following assumptions:

- 1- No unmeasured confounding in the adjusted relationship Exposure-Outcome
- 2- No unmeasured confounding in the adjusted relationship Mediator-Outcome
- 3- No unmeasured confounding in the adjusted relationship Exposure-Mediator
- 4- No confounding of the Mediator-Outcome relationship that is an effect of the exposure, irrespective of whether that variable is available

Assessment

Following VanderWeele and Vansteelandt⁴⁰, I used inverse probability weighting to estimate NDE and NIE. Inverse probability weighting provides estimates of marginal effects, that is, effects that are averaged over covariates. The approach requires the estimation of three counterfactuals or potential outcomes: $P(Y_{a Ma^*} = 1|c)$, $P(Y_{a^* Ma^*} = 1|c)$, and $P(Y_{a Ma} = 1|c)$ (see above the definition of NDE and NIE based on these counterfactuals)

To estimate $P(Y_{a^* Ma^*} = 1|c)$ I first fit a covariate adjusted model for the outcome (Y) using multiple logistic regression including A*M interaction terms when appropriate. I then obtained a weighted average of the estimated probabilities of outcome=1 among unexposed participants, giving each participant the weight $w_1 = P(A=0) / P(A=0|Cov)$. Similarly, to estimate $P(Y_{a Ma} = 1|c)$, I obtained a weighted average of the estimated probabilities of outcome=1 among exposed participants where each subject was given the weight $w_2 = P(A=1) / P(A=1|Cov)$. Conditional and unconditional probabilities of A=0 or A=1 were estimated using logistic regression. To estimate $P(Y_{a Ma^*} = 1|c)$, I used the logistic regression coefficients obtained earlier from the full-model for the outcome Y to estimate the $P(Y=1)$ in the subsample comprised by the unexposed participants (A=0), to whom I switched their exposure status to exposed (A=1) while keeping the values for covariates and mediators they had as unexposed subjects. I then obtained the weighted average of the predicted values for $P(Y=1)$ under those conditions, giving each subject the weight $w_3 = 1 / (1 - P(A=1|Cov))$. See corresponding SAS code in the Appendix section A.3.1.

These three counterfactuals were estimated for each of the mediation models and for each model NDE and NIE were estimated as:

$$NDE = P(Y_{a Ma^*} = 1|c) / P(Y_{a^* Ma^*} = 1|c)$$

$$NIE = P(Y_{a Ma} = 1|c) / P(Y_{a Ma^*} = 1|c)$$

I bootstrapped to obtain 95% confidence intervals for the estimates of natural effects.

In addition, for each mediation analysis, I estimated the “Proportion Mediated” as: $OR^{NDE} \times (OR^{NIE} - 1) / (OR^{NDE} \times OR^{NIE} - 1)$.

In secondary analysis I investigated whether our results were possibly being unduly influenced by the presence of dietary mis-reporters. I did this by reassessing mediation in a subsample comprised of the participants (N= 2,460) that I classified as plausible dietary reporters based on our application of the method by Huang et al. described above. In further analysis in this subsample, I evaluated whether total caloric intake was possibly a mediator, regardless of diet composition. To test this, I added the variable kilocalories per day and a variable for height at age 13 years, as caloric requirements are known to vary by age, sex, and height.

All tests conducted in these analyses that involved the study outcome (high triglycerides), including bivariate association tests, regression models, are adjusted by means of IPCW to account for the effects of participant attrition through study follow-up. In mediation analysis, as per our approach, data was weighted for the probability of exposure, and mediators. SAS code for mediation analysis can be found in Appendix A.4.2. Mediation analyses were repeated with each one of 5 imputed datasets and results were essentially the same. Results obtained with imputed dataset # 1 are presented. All statistical analyses were conducted with SAS 9.4.

Results

Characteristics of study participants and the relationship of study variables with triglyceride levels at end of study (Table 3.1)

This study sample was 50% female/male and overwhelmingly white (95%). Only 5% of participants were obese; 11 percent of the participants had clinically high levels of triglycerides, the study outcome, at the end of follow-up, with no apparent differences between male and females; at baseline, 11% of the participants met the study definition of hyperactivity problems and 17 % met the definition of conduct problems. Adolescents with high levels of triglycerides were significantly more likely to have had hyperactivity (16 % vs 10 %, $p < .05$), or conduct problems (23% vs 16%, $p < .05$) at baseline. They were slightly more likely to be white (98% vs 96%, $p < .05$), their mothers were younger at birth (28.8 years vs 29.4 years, $p < .05$), had higher educational attainment at study baseline (57% vs 49%, $p < .05$), and were heavier before pregnancy (62.5 kg vs 60.2 kg, $p < .05$). Participants with high levels of triglycerides were less likely to had been breastfed for more than 3 months (50% vs 59%), or to had been breastfed at all (76% vs 80%), $p < 0.05$. During follow-up, at age 13 years, they consumed diets with lower percent of energy (E) from fats (34.9 % E from fat vs 35.5% E from fat, $p < .05$), had a slightly higher unsaturated/saturated (unsat/sat) dietary fats ratio (38 % unsat/sat vs 37 % unsat/sat, $p = 0.08$), and a higher intake of alcohol (0.35 g/day vs 0.26 g/day $p = 0.07$). They had higher BMIs at age 8 (17.7 BMI units vs 17.0 BMI units, $p < .05$), had a larger increase in BMI between ages 8 and 15 years (5.5 BMI units vs 4.2 BMI units $p < .05$), and were more likely to be obese at age 15 (17% vs 4%, $p < .05$) than adolescents with triglycerides within normal levels. They were slightly less likely than peers to provide plausible dietary reports (37 % vs 42%, $p = 0.08$).

Bivariate relationships of hyperactivity and conduct problems with mediator variables

(Table 3.2)

Participants with hyperactivity or conduct problems at baseline slept slightly less than their peers at age 10 (hyperactivity: 10.34 hours vs 10.44 hours, $p < .05$, conduct problems: 10.40 hours vs 10.43 hours, $p = 0.18$). At age 13, they consumed significantly more sugar sweetened beverages per day (hyperactivity: 0.78 servings vs 0.47 servings, $p < .05$, conduct problems: 0.61 servings vs 0.49 servings, $p < .05$), were more likely to consume alcohol, especially youth with conduct problems (hyperactivity: 19% vs 16%, $p = 0.15$, conduct problems: 21% vs 16%, $p < .05$), and were more physically active than their peers, in particular those of them with hyperactivity (hyperactivity: 589 cpm vs 551 cpm, $p < .05$, conduct problems: 570 cpm vs 552 cpm, $p < .05$). Neither the children with hyperactivity (40.5% vs 41.8%, $p = 0.64$) or with conduct problems (41.2% vs 41.7%, $p = 0.84$) were more likely than their peers to provide implausible dietary reports. Participants with conduct problems were more likely than peers to smoke at age 15 (38% vs 29%, $p < .05$). Youth with hyperactivity problems had BMI at age 8 similar to that of peers, but they experienced a larger increase in BMI through follow-up (4.6 BMI units vs 4.3 BMI units, $p < .05$), and were significantly more likely to be obese at age 15 (17% vs 10%, $p < .05$). A similar trend was observed when comparing youth with conduct problems to their counterparts, except that participants with conduct problems were already slightly heavier at age 8 (17.3 BMI units vs 17.1 BMI units, $p < .05$). I compared (not shown in tables) baseline levels of triglycerides (geometrical means) in children with hyperactivity, and children with conduct problems, with their respective counterparts in a subsample of participants who attended the age 7 years clinic, $n = 2353$, for whom fasting measures of triglycerides were available. I did not find differences in triglyceride levels

across these groups at baseline (hyperactivity, $p= 0.95$, conduct problems, $p= 0.34$).

Multivariate regression modeling of the relationship of hyperactivity and conduct problems with triglycerides (Table 3.3)

In multivariable logistic regression analysis, hyperactivity and conduct problems were each associated with high triglycerides and the relationships remained after control for confounding. Compared with non-hyperactive participants, those who had hyperactivity at study baseline had almost twice the odds of developing high triglyceride levels by adolescence (OR= 1.81 (95% CI: 1.34 – 2.44) in models that adjusted for sex, age, and race; and in a model that further adjusted for maternal education, maternal age at delivery, maternal depression score, the child's birth weight, gestational age at birth, and breastfeeding (OR= 1.74 (95% CI: 1.29 – 2.37)). The corresponding relative odds for youth with conduct problems were OR= 1.62 (95% CI: 1.25 – 2.10) for the minimally adjusted model and OR= 1.60 (95% CI: 1.23 – 2.09) for the fully adjusted model.

Mediation of the relationship of hyperactivity and conduct problems with triglycerides (Table 3.4)

In analyses that used inverse probability weighting to assess the role of BMI and health behaviors in mediating the effects of hyperactivity on triglycerides, the total average effect of hyperactivity (averaged over covariates) was estimated to be OR= 1.63 (95% CI: 1.24 – 1.99). Note that this effect estimate varies slightly with the one obtained from regression models (reported in the section above). This difference is due to the weighting of data used for assessment of mediation. By weighting of data we estimate the effect of the exposure on the outcome averaged over the actual values of covariates in the sample. In contrast, the effect we estimate from

regression models is the effect of exposure on the outcome when all covariates take their reference level. Mediators were then added to the model, in a sequential fashion (See Fig. 3.2), and at each step, the estimated indirect effect indicated the effect of hyperactivity that was mediated by the combination of mediators in the model. No evidence was found of indirect effects mediated by BMI at age 8, health behaviors at ages 10-13 years, and BMI changes over follow-up and obesity at age 15, as these mediators were sequentially added to the model. In the last step, smoking at age 15 was added and with its additional contribution the total estimated indirect effect was OR=1.08 (95% CI: 0.98 – 1.14), a very small effect that would account for only 19.6 % of the total effect of hyperactivity. The same strategy was applied for the assessment of mediation of the effect of conduct problem on triglycerides. The total, average effect of conduct problems on triglycerides was OR= 1.50 (95% CI: 1.21 – 1.93). I found no evidence of any significant mediated effects as I sequentially added BMI at age 8, health behaviors 10 – 13 years, BMI change and obesity at age 15 and smoking to the model. The total estimated effect mediated jointly by these mediators was only OR= 1.07 (95% CI: 0.98 – 1.14) explaining at most only about 19 % of the total average effect of conduct problems on triglycerides.

The estimates of mediated effects were essentially the same in secondary analyses conducted in a subsample (42 % of the full sample) of plausible dietary reporters (not shown). In these analyses the role of caloric intake was additionally assessed but no evidence was found to support that pathway.

Discussion

This research investigated whether childhood hyperactivity and conduct problems had a direct effect on adolescent levels of triglycerides, a biomarker that is causally related to coronary heart disease⁴¹. I used causal-mediation methods to estimate indirect effects, defined in this study, as the effects that work through pathways involving health behaviors and BMI, and direct effects, defined as all other pathways not involving those mediators. I also estimated the relative contribution of those pathways to the total effects of hyperactivity and conduct problems on triglycerides.

The results suggest that hyperactivity and conduct problems influence triglycerides levels mainly by direct effects. I did not find evidence of any significant indirect effects explained by the mediators examined. At most, about 20% of the total effects might have been mediated jointly by BMI status, BMI changes, and by health behaviors including, diet, physical activity, alcohol intake, and smoking. Furthermore, the small indirect effects would seem to be mostly driven by BMI, with no contribution from health behaviors, aside from a small effect of smoking. Overall, the pathways appear to be similar for hyperactivity and conduct disorder, except that early BMI (at age 8) and smoking at age 15 might have played a more important role in mediating the overall effect of conduct problems than of the effects of hyperactivity.

Based on the findings of prior studies suggesting associations of externalizing behaviors with body adiposity and unhealthy eating^{16,17,20}, sedentary lifestyle¹⁸, and substance use²², and the extensive prior evidence of strong relationships of body adiposity⁴², and of aspects of diet⁴³ and physical activity with triglycerides⁴⁴, I had expected to find larger estimates of indirect effects. I had hypothesized that sleep, diet, and physical activity would be important drivers of the total effects, while adolescence BMI would explain a smaller portion once childhood BMI and health

behaviors in childhood had been taken into account.

In these analyses, BMI at ages 8, and 15, obesity at age 15, and BMI change were each associated with hyperactivity, conduct problems and with triglycerides in bivariate associations. However, in IPW models that accounted for a wide range of confounders and for bias from study attrition, BMI variables did not seem to play an important role in mediating the relationships of hyperactivity and conduct problems with triglycerides. Some prior studies have found BMI to be an important mediator of similar relationships with Framingham CVD risk score¹⁰, hypertension¹¹ and carotid artery calcification in adulthood⁴⁵. Discrepancies between our findings and those studies might be explained by differences in timing at outcome assessment (adolescence vs adulthood), examination of different CVD-related outcomes, due to differences in prevalence of obesity and of unhealthy behaviors, and due to different methodological approaches of accounting for confounding and other sources of bias. For example, the prevalence of obesity in this cohort was very low compared with the current obesity prevalence among US adolescents (5 % vs 21%, NHANES 2015-17). However, some more recent studies that reported associations of other common mental health problems with type-2 diabetes and CVD in US-based cohorts of young adults and older adults have also failed to find a significant role of BMI and unhealthy behaviors in mediating those associations⁴⁶⁻⁴⁸.

My findings of no mediation by health behaviors were not surprising given my observations of very weak associations of health behavior variables with triglycerides, and the almost across-the-board null associations of dietary variables (with the exception of SSB) with hyperactivity and conduct problems. These null associations could reflect true, null causal relationships, or could have resulted from error in the measurement of health behavior variables.

In the case of dietary assessment, it is likely that the results from the analysis conducted in the full sample were biased due to error in measurement of diet. This is indicated by the finding of an inverse association of self-reported energy with BMI, a finding that is counterintuitive for a non-clinical sample. However, these results didn't change when I replicated the analysis in the subsample of "plausible" dietary reporters. Findings of associations between diet and markers of CVD risk including BMI, from other studies in the ALSPAC sample, have been inconsistent, with associations found to be unstable over time. One such study found that adherence to the "Processed" and "Packed lunch" dietary patterns at age 7 was associated with BMI at age 17, however, adherence to those dietary patterns at ages 10 and 13 did not associate with BMI. Furthermore, there were no associations between any of the dietary patterns at ages 7, 10, or 13, with either of blood pressure, blood lipids, or glucose at age 17^{27,29}. Two other studies in ALSPAC investigated the prospective relationship of SSB with body adiposity. In one of them, SSB at ages 5 or 7 was not associated with fatness at age 9²⁹, but in the other study⁴⁹, change in SSB intake from 10- to 13-years was associated with increased BMI at age 13.

Sleep did not contribute to mediation of the main effects in this study, which was internally consistent given that sleep was not associated with triglycerides, and although statistically significant, the difference in sleep hours between children with hyperactivity or conduct problems with their study peers were very small. This lack of variation probably owes to the fact that in the ALSPAC cohort sleep hours are in general very high. For illustration, at age 10, in the years 2000-02, these children slept significantly longer hours than did same-age US children in 1997⁵⁰. Participants in our sample who ranked at the bottom 10th percentile of sleep hours slept significantly more (9.6 hours vs. 8 hours) than did children at the 10th percentile of sleep hours in the US general pediatric population⁵⁰. Furthermore, hyperactive children in our study who ranked

below the 5th percentile of sleep hours among hyperactive children (that is, the hyperactive children who slept the least among hyperactive children) still slept more (8.3 hours versus 8 hours) than did US children of the general population who ranked higher, at the 10th percentile. ALSPAC children also slept longer hours compared with more recent UK cohorts. In a study that compared sleep hours at age 14 between ALSPAC participants who were 14 in 1995, and participants in the Millennium Cohort Study who were 14 in 2005, showed that the % of teens that slept fewer than 8 hours/day grew from 5.7 in 1995 (ALSPAC) to 13.4 in 2005 (Millennium Cohort Study).

Contrary to what I had expected, physical activity was, if anything, a negative mediator. I found that children with externalizing behaviors were more, not less, physically active than their peers. Physical activity had a small inverse relationship with triglycerides, therefore in this sample, physical activity was possibly a pathway through which hyperactivity and conduct problems might have reduced triglycerides. It's been posited that children with low self-control would be less likely to engage in group-based structured physical activity that requires self-control and involves social interaction⁷. Based on this theory and the known negative effects of physical inactivity on blood lipids⁴⁴, I had hypothesized that low physical activity would be a mediator (positive). However, it is also entirely plausible that the elevated motor activity that children with externalizing problems sustain throughout the day more than compensates for the lack of time spent on group-based physical activity, to achieve the higher daily total counts of physical activity that I observed among these children, compared with their study peers.

Clinical evidence shows that at any given point, triglyceride values are reflective of the person's recent (past few months) diet, physical activity, and smoking^{43,44,51}. Thus, for childhood health behaviors to be mediators of the association of childhood externalizing problems with triglycerides at age 17, differences in health behaviors between children with and without

externalizing problems should persist into age 17. It is plausible, however, that these differences in health behaviors become insignificant by adolescence as youth gain independence and greater control over their diet and lifestyle choices and poor choices become more normative. The erasing of the differences in unfavorable health behaviors among children with and without externalizing problems might explain our observation that health behaviors assessed before adolescence were associated with childhood hyperactivity and conduct problems but not with triglycerides at age 17.

Alternatively, it is possible that the children that are at higher risk of developing high triglycerides are in fact the subset of children with childhood externalizing problems that persist into adolescence, or the predominantly hyperactive, or inattentive types⁵², which I did not discriminate among in this analysis. This subset of children might be more likely to adopt unfavorable and persisting health behaviors and to do so at higher levels, with a more significant clinical impact on triglyceride levels.

Finally, these findings may lend support to the alternative main hypothesis that the relationships between externalizing problems with triglycerides might be mediated by neurochemical effects associated with dysregulation of the SNP and HPA-axis, the body's system for response and adaptation to acute and chronic stress, observed among both adult and pediatric externalizing disorders⁵³⁻⁵⁶. Stress-mediated persistent activation of the HPA axis leads over time to dysfunction and alteration of glucocorticoid pathways and metabolism with consequences for the immune and endocrine systems linked to increased cardiometabolic risk. Alterations of the immune system reflected by elevated levels of Interleukin-6 and fibrinogen have been documented in children exposed to chronic levels of stress^{57,58} and among children with externalizing behavior problems⁵⁹. Chronic high levels of inflammation induce changes in lipids profiles, including the increase in blood concentrations of triglycerides⁶⁰. Furthermore, It is posited that childhood

chronic stress could act as a modifying factor in the maturation process of the still plastic SNP and HPA axis thus becoming embedded in a lasting fashion, with life-long effects on the body's vulnerability to chronic disease^{61,62}.

These results should be considered in the context of some study-specific limitations. First, I relied on parent's reports, rather than clinical interviews, for the assessment of participant's externalizing problems. However, the SDQ is a well-validated tool for use in large epidemiological studies and I considered it appropriately valid and precise for the goals and the context of the research. Second, I did not have baseline values of study outcome for the entire study sample and relied on a secondary analysis on a subsample of participants for whom those measures were available to infer that triglyceride levels did not vary between participants with and without externalizing problems at baseline. Third, as an observational study, this one is liable to bias due to unmeasured confounding. For example, I did not adjust for use of psycho-stimulant drugs, which are commonly used to treat children with hyperactivity and low self-control. However, these drugs have been shown to reduce levels of triglycerides⁶³, therefore, if anything, these results are biased to the null and our effect estimates are conservative. I controlled for maternal biological family history of CVD and diabetes but I did not have information on paternal family history, therefore results may bear some confounding resulting from this omission. Overall, however, my strategy for control of confounding was robust and the results are essentially valid. Fourth, like most life-course studies, ALPSAC suffered from significant attrition (50%). Unlike most studies however, I used inverse probability of censoring weighting in all my analyses, and this approach likely reduced some of the bias created by attrition. Lastly, and as discussed above, this sample was significantly healthier than contemporary US cohorts and more recent UK cohorts with regards to BMI and health behaviors hypothesized in this study to be mediators. These factors may contribute

more importantly to mediation of main effects in less healthy cohorts. For example, in U.S cohorts that include more disadvantaged segments of the population, including ethnic minorities, children of parents with less education, and less social and financial resources, poor health behaviors will likely be more prevalent and have a greater role in mediating the relationships studied in this research.

This study had also numerous important advantages including the use of a large, population-based birth-cohort, known for the quality of its assessments and data. I relied on two separate assessments of the participant's externalizing problems to be able to identify both, earlier and later onset cases. Unlike most similar and prior studies investigating mediation, this study had an ideal design, whereby mediator variables were assessed in the middle of the follow-up period, preserving temporal relationships and thus improving our ability for drawing causal inferences. My approach to confounding control was robust and more comprehensive than in most other studies, addressing a wide range of factors including family history of cardiovascular disorders, socio-economic status, maternal factors including body adiposity, history of mental health, education, pregnancy outcomes, birth and childhood outcomes strongly associated with cardiovascular health later in life, including breastfeeding. I applied state-of-the-art methods for assessment of mediation that allowed me to account for exposure-mediation interactions and the estimation of natural effects with a more readily causal interpretation. I was able to assess all the most important health behaviors thought to be implicated in the main effects, including objectively assessed measures of physical activity and body adiposity.

In summary, this study shows solid evidence that a history of childhood externalizing problems is directly associated with a moderate increased risk of developing clinically high levels of triglycerides by adolescence, regardless of body adiposity and the known propensity among

children with externalizing symptoms to the adoption of unhealthy behaviors. These findings have critical implications for clinical and research practice. First, they suggest that health practitioners may need to start assessing triglyceride levels in adolescents with a history of childhood hyperactivity or conduct problems, even among adolescents with healthy weight, and especially among children not treated with psycho-stimulants (known to reduce triglycerides). These children might require dietary modifications –or other appropriate approaches- that specifically target triglycerides but not body weight. Second, future research studies should seek to replicate these findings in more recent cohorts known to bear much higher prevalence of obesity and unhealthy health behaviors. Third, future studies should also seek to obtain repeated assessments of health behaviors throughout follow-up, especially given that health behavior norms change from childhood to adolescence. Conducting repeated assessments of these behaviors would be necessary to disentangle temporal variations in health behaviors that are due to normative, age-related changes and changes that are due to the influence of externalizing problems. Fourth, future studies should also examine whether the risk of high triglycerides varies among adolescents with childhood-limited, adolescence-onset, and childhood-onset persistent externalizing problems, and whether different phenotypic sub-types including inattentive, hyperactive, and more antisocial types, differ in their associations with health behaviors and CVD risk. Future studies should include measures that allow the characterization of these subtypes using stratified sampling approaches to ensure adequate power to study these relationships.

These findings also clearly warrant more and expanded research on mechanisms linking childhood externalizing problems with triglycerides other than health behaviors and body adiposity. Over the past decade a growing literature has examined disruption of the SNP-HPA in children and adolescents with externalizing psychopathology. The research suggests that these

changes in SNP-HPA and downstream pathways might also vary over time⁶⁴, which further adds to the formulation made above that, in order to significantly expand our understanding of these associations and the mechanisms that underlie them, next studies must rely on repeated assessments of mediator variables. If, as our study suggests, externalizing problems influence triglyceride levels mainly by neurochemical pathways, that is, regardless of body adiposity and health behaviors, additional new research would be needed to investigate what therapeutical approaches, including perhaps anti-inflammatory treatments, might be effective in reducing high triglyceride levels among these children.

Figures and Tables

Figure 3. 1: Study Di-acyclic Graph. The hypothesized main causal relationship of hyperactivity or conduct problems with triglycerides is depicted by red line. Mediator variables are shown in blue. Time at assessment of study variables is shown in parentheses. Mediating pathways are shown in solid black lines, and confounding pathways are shown in dash lines

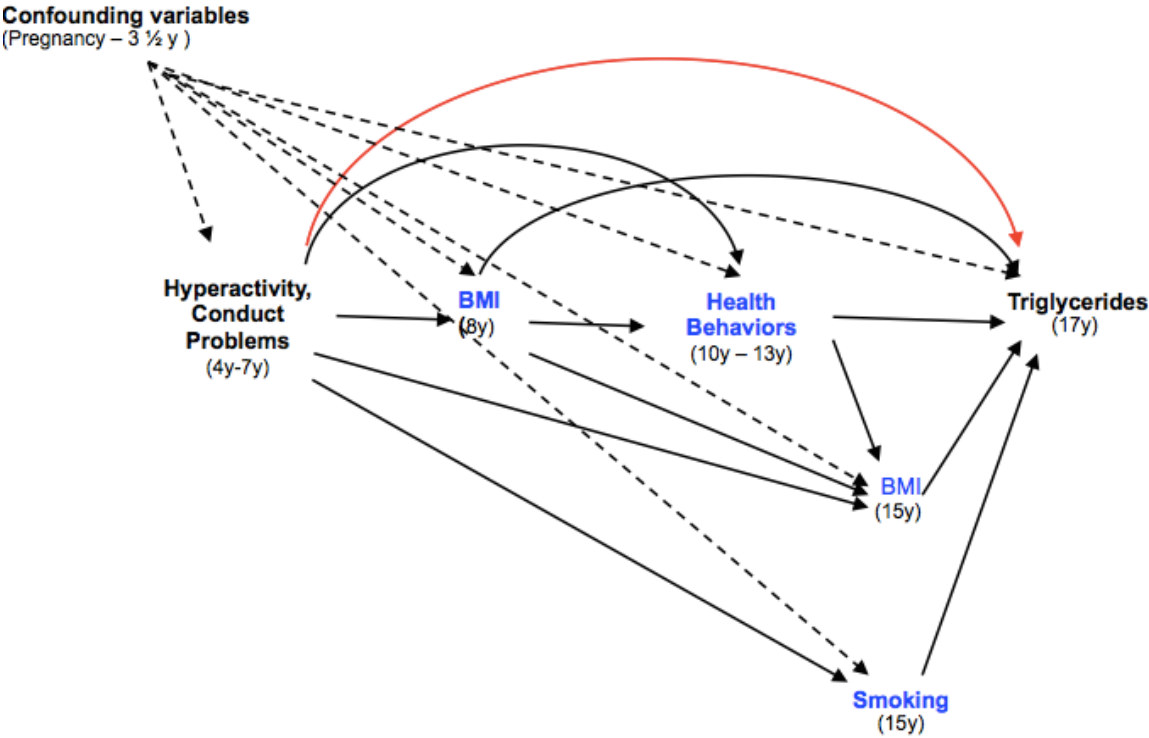


Figure 3. 2: Mediation analysis using a sequential approach: At each step (model #), mediators that are added to the model are shown in red.

Models	NDE	NIE
1	$HP \rightarrow TG +$ $HP \rightarrow HB \rightarrow TG +$ $HP \rightarrow HB \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow SMK \rightarrow TG$	$HP \rightarrow BMI_8 \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow HB \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow BMI_{15} \rightarrow TG$
2	$HP \rightarrow TG +$ $HP \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow SMK \rightarrow TG$	$HP \rightarrow BMI_8 \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow HB \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow HB \rightarrow TG +$ $HP \rightarrow HB \rightarrow BMI_{15} \rightarrow TG$
3	$HP \rightarrow TG +$ $HP \rightarrow SMK \rightarrow TG$	$HP \rightarrow BMI_8 \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow HB \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow HB \rightarrow TG +$ $HP \rightarrow HB \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow BMI_{15} \rightarrow TG$
4	$HP \rightarrow TG$	$HP \rightarrow BMI_8 \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow HB \rightarrow TG +$ $HP \rightarrow BMI_8 \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow HB \rightarrow TG +$ $HP \rightarrow HB \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow BMI_{15} \rightarrow TG +$ $HP \rightarrow SMK \rightarrow TG$

* BMI₈ = BMI at age 8 y, HB = Health Behaviors (Sleep at age 10y, diet, sugar-sweetened beverages, alcohol, and physical activity at age 13y), BMI₁₅ = BMI at age 15y, SMK = Smoking at age 15 y.

Table 3. 1: Characteristics of study participants

	N (%)	BMI		Triglycerides		
		Below CDC-95 th percentile	At or above CDC-95 th percentile	< 130 mg/dl	≥ 130 mg/dl	
Total, N (%)	3446 (100%)	3273 (95)	173 (5)	3068 (89)	378 (11)	
Behavior Problems at ages 4 or 7 years		N (%)		<i>P</i> *	N (%)	<i>P</i> *
Hyperactivity problems				.008		< .001
Never	3079 (89)	2934 (90)	144 (83)		2763 (90)	316 (84)
Ever	367 (11)	339 (10)	29 (17)		305 (10)	62 (16)
Conduct problems				.003		< .001
Never	2869 (83)	2746 (84)	130 (75)		2579 (84)	289 (77)
Ever	577 (17)	527 (16)	43 (25)		489 (16)	88 (23)
Study covariates (Before age 4 y)		N (%)		<i>P</i> *	N (%)	<i>P</i> *
Sex,				.630		.850
Male	1707 (50)	1622 (50)	89 (51)		1519 (50)	189 (50)
Female	1739 (50)	1651 (51)	84 (49)		1549 (50)	189 (50)
Race/ethnicity				.592		.045

Table 3.1 Cont'd

Non-white	131 (4)	125 (4)	8 (5)		124 (4)	8 (2)	
White	3315 (96)	3148 (96)	165 (95)		2944 (9)	370 (98)	
Maternal education				< .001			.003
Below 'O' level	1730 (50)	1669 (51)	61 (35)		1568 (51)	162 (43)	
At or above 'O' level	1716 (50)	1601 (49)	112 (65)		1501 (49)	215 (57)	
Household income / week				< .001			.180
<200	658 (19)	610 (19)	49 (28)		581 (19)	78 (21)	
200-399	1796 (52)	1700 (52)	94 (55)		1589 (52)	207 (55)	
400+	992 (29)	963 (29)	30 (17)		898 (29)	93 (25)	
Family history of diabetes, Yes	142 (4)	139 (4)	8 (5)	.811	131 (4)	12 (3)	.277
Family history of hypertension, Yes	1155 (34)	1126 (34)	59 (34)	.936	1026 (33)	129 (34)	.787
Family history of heart disease, Yes	439 (13)	425 (13)	21 (12)	.747	390 (13)	49 (13)	.837
Maternal diabetes				.062			0.370
Never diagnosed with diabetes		3134 (96)	163 (94)		2931 (96)	364 (97)	
Ever diagnosed with diabetes		139 (4)	10 (6)		137 (4)	14 (3)	
Gestational weight gain				.050			.237
Below-	442 (13)	412 (13)	21 (12)		388 (13)	53 (14)	

Table 3.1 Cont'd

Within-	1061 (31)	1051 (32)	41 (24)		958 (31)	102 (27)	
Above-	1943 (56)	1810 (55)	111 (64)		1722 (56)	222 (59)	
recommended							
Gestational hypertension, Yes	540 (16)	500 (15)	37 (21)	.031	489 (16)	51 (14)	.249
Breastfeeding				.004			.021
Never	688 (20)	526 (16)	37 (21)		600 (20)	89 (24)	
< 3 months	773 (22)	657 (20)	48 (28)		673 (22)	99 (26)	
3-5 months	599 (17)	583 (18)	30 (17)		545 (18)	54 (14)	
6+ months	1386 (40)	1507 (46)	50 (26)		1250 (40.8)	136 (36)	
Small for gestational age, Yes	307 (9)	292 (9)	15 (9)	0.910	291 (10)	32 (9)	0.554
Large for gestational age, Yes	427 (12)	396 (12)	31 (18)	0.024	375 (12)	36 (10)	0.123
Preterm birth, Yes	179 (5)	173 (5)	6 (4)	0.294	157 (5)	19 (5)	0.990
		Mean (SD) or Median (IQR)		<i>P</i> *	Mean (SD) or Median (IQR)		<i>P</i> *
Age, years, mean	-	15.5 (.3)	15.5 (.3)	.215	17.1 (1.1)	17.2 (1.1)	.060
Neighborhood stress index, mean	3.7 (3.2)	3.7 (3.2)	4.4 (4.1)	.070	3.7 (3.2)	3.8 (3.6)	.806
Maternal age at delivery, mean	29.3 (4.4)	29.5 (4.4)	28.9 (4.3)	.122	29.4 (4.4)	28.8 (4.5)	.009
Maternal weight before pregnancy, mean (Kg)	60.4 (10.0)	59.7 (11.1)	71.8 (18.3)	< .001	60.2 (11.7)	62.5 (14.0)	.002

Table 3.1 Cont'd

Maternal depression score, median (IQR)	50 (6.0)	5.0 (6.0)	5.0 (6.0)	.310	5.8 (4.6)	5.4 (4.2)	.095
Birthweight (g), mean	3429 (539)	3432 (541)	3545 (530)	.008	3433 (543)	3390 (496)	.147
Gestational age (weeks), mean	39.5 (1.8)	39.4 (1.8)	39.6 (1.4)	.181	39.5 (1.8)	39.5 (1.7)	.858
Mediator variables	N (%)			<i>P</i> *	N (%)		<i>P</i> *
Cigarette smoking, Yes	1049 (30)	984 (30)	57 (33)	.354	923 (30)	127 (34)	.161
Alcohol, Yes	572 (17)	530 (16)	32 (18)	.424	498 (16)	74 (20)	.104
Dietary reporting				< .001			.136
Under-reporter	1249 (36)	1136 (35)	109 (63)		1095 (36)	155 (41)	
Plausible reporter	1456 (42)	1402 (43)	51 (29)		1308 (42)	147 (39)	
Over-reporter	740 (21)	735 (23)	13 (8)		665 (22)	75 (20)	
		Mean (SD) or Median (IQR)		<i>P</i> *	Mean (SD) or Median (IQR)		<i>P</i> *
SSB, servings/day, median	0.51 (1.57)	0.51 (1.55)	0.37 (1.39)	.097	0.51 (1.54)	0.51 (1.65)	.421
% Calories from fat, mean	35.5 (5.8)	35.5 (5.8)	35.4 (6.4)	.927	35.6 (5.8)	34.9 (6.0)	.037
% Calories from carbohydrates, mean	53.4 (6.4)	53.5 (6.4)	52.6 (7.5)	.083	53.4 (6.4)	53.8 (6.8)	.214
Unsat. fats/ Sat. fats ratio %, mean	34.4 (6.5)	38 (6)	36 (6)	.012	37 (6)	38 (6)	.080
Kcal/day, mean	1960 (506)	1971 (504)	1839 (546)	.083	1964 (504)	1928 (521)	.192

Table 3.1 Cont'd

Alcohol, gr/day, mean	0.27 (0.83)	0.27 (.81)	.31 (91)	.662	0.26 (.81)	0.35 (.96)	.068
Sleep, average hours/ day, mean	10.4 (0.62)	10.4 (.6)	10.4 (.7)	.780	10.4 (.6)	10.4 (.6)	.548
PA, average CPM, mean	555 (183)	556 (184)	530 (168)	.071	557 (184)	541 (175)	.117
BMI, age 8 y	17.1 (2.3)	16.9 (2.1)	21.3 (2.9)	< .001	17.0 (2.3)	17.7 (2.8)	< .001
Change in BMI, ages 8y to 15y, mean	4.3 (2.4)	4.0 (2.1)	9.5 (3.2)	< .001	4.2 (2.3)	5.5 (3.2)	< .001
BMI at age 15, at or above CDC- 95 th percentile, Yes	173 (5)	-	-	-	109 (4)	56 (17)	< .001

Inverse probability of censoring weights (IPCW) were applied to all tables and tests

Table 3.2: Relationship of Hyperactivity and Conduct Problems with Health Behavior variables, bivariate associations

		Health Behavior Mediators									
		N=3446									
Behavior		Average # sleep hours		# SSB servings per day ^{2,4}		Uses alcohol, Yes ^{3,4}		PA, Average CPM ^{1,4}		Smoking, Yes ^{3,4}	
Problem		per day ^{1,4} ,									
Age at		10 y		13 y		13 y		13 y		15 y	
assessment											
	N (%)	Mean (SD)	<i>p</i>	Median (IQR)	<i>p</i>	N (%)	<i>p</i>	Mean (SD)	<i>p</i>	N (%)	<i>p</i>
Hyperactivity											
Problems											
No	3078 (89)	10.44 (.62)	.005	0.47 (1.49)	< .001	501 (16)	.152	551 (183)	< .001	934 (30)	.608
Yes	360 (11)	10.34 (.63)		0.78 (1.83)		71 (19)		589 (177)		116 (32)	
Conduct											
Problems											
No	2869 (83)	10.43 (.61)	.182	0.49 (1.48)	< .001	450 (16)	.002	552 (183)	.038	830 (29)	< .001
Yes	577 (17)	10.40 (.67)		0.61 (1.71)		121 (21)		570 (182)		219 (38)	

¹ Differences of means were assessed by T-tests.

² Differences of medians were assessed by Wilcoxon tests

³ Differences of proportions were assessed by Chi-Square tests.

⁴ Inverse probability of censoring weights (IPCW) were applied to all tables and test

Table 3.3: Relationship of Hyperactivity and Conduct Problems with Triglycerides.

Logistic regression models

Behavior problem ¹	Triglycerides		Model 1 ^{1,3}	Model 2 ^{2,3}
	< 130 mg/dl	≥ 130 mg/dl	OR (95 % CI)	
Hyperactivity problems				
Never	2764	315	1.00 (Ref)	1.00 (Ref)
Ever	305	62	1.81 (1.34-2.44)	1.74 (1.29 - 2.37)
Conduct problems				
Never	2580	289	1.00	1.00
Ever	489	88	1.62 (1.25 – 2.10)	1.60 (1.23 – 2.09)

Hyperactivity Problems and Conduct Problems were modeled separately.

¹ Model 1 is adjusted for age, sex, and race/ethnicity.

² Model 2 is adjusted as model 1 plus maternal education, maternal age at delivery, maternal depression, child's birthweight, gestational age, and breastfeeding.

³ Inverse probability of censoring weights (IPCW) were applied to all models.

Table 3.4: Mediation of the relationships of Hyperactivity and Conduct Problems with Triglycerides by health behaviors and BMI. Odds Ratios (95% CI) for the marginal (averaged over covariates) Natural Direct (NDE), Natural Indirect (NIE), and Total Effects (TE)

Mediators in Model	Hyperactivity Problems				Conduct Problems			
	NDE	NIE	TE	PM (%)	NDE	NIE	TE	PM (%)
	OR (95% CI)				OR (95% CI)			
None	-	-	1.63 (1.24 – 1.99)	-	-	-	1.50 (1.21 – 1.93)	-
M1=BMI 8y	1.61 (1.24 – 2.01)	1.00 (0.96 – 1.03)	1.61 (1.23 – 1.97)	0.6	1.46 (1.17 – 1.84)	1.02 (0.99 – 1.06)	1.50 (1.21 – 1.93)	7
M1 + M2= Health Behaviors 10-13 y	1.61 (1.26 – 2.03)	1.01 (0.93 – 1.04)	1.61 (1.23 – 1.95)	1.4	1.46 (1.17 – 1.83)	1.02 (0.97 – 1.05)	1.49 (1.20 – 1.92)	6.3

Table 3.4 Cont'd

M1 + M2 + M3=	1.49	1.07	1.60	18.3	1.41	1.06	1.49	16.7
Obesity 15y and BMI change	(1.13 – 1.89)	(0.96 – 1.13)	(1.23 – 1.93)		(1.11 – 1.75)	(0.97 – 1.12)	(1.21 – 1.90)	
M1 + M2 + M3 +	1.48	1.08	1.60	19.6	1.40	1.07	1.49	19.3
M4= Smoking 15y	(1.12 – 1.89)	(0.98 – 1.14)	(1.23 – 1.93)		(1.10 – 1.72)	(0.98 – 1.14)	(1.20 – 1.88)	

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Appendix for Chapter 3

Figure A.3. 1: Causal mediation analysis -SAS code

Hp,Counterfactual 1= P (YaMa=1|cov); *Estimated conditional probabilities of each exposure statuses.

Creates a dataset with a variable for those probabilities;

```
proc logistic data=mydata ;
class everHP(ref='0')/param=ref;
class race(ref='1')/param=ref;
class momed(ref='1')/param=ref;
class sex kc404;

model everhp= sex race agechol momed depression bwt bestgest momagedel
kc404 ;

score data=mydata out=preda;

run;

data preda;*In the dataset PREDA, it gives the name pal to the variable
prbability exposure=1;
set preda;
pal=P_1;*Conditional probability of being E+=Propensity score;
run;

data mydata0; *Creates a dataset that is copy of the original but the
exposure is set to - to everyone;
```

```

set mydata;
everHP=0; output;

run;

data mydata1; *Creates a dataset that is copy of the original but the
exposure is set to + to everyone;
set mydata;
everHP=1; output;

run;

*bmic8 bmi15 ssb13_new smokes avgsleephr13 pctfat fg13kcal fatratio fg3100
age13mos;
*avgsleephr everHP*avgsleephr pctfat pctcho fatratio alcocat everhp*alcocat
smokes cpm13
ssb13_new fg13kcal fg3100 bmic8 cdcBMI95;

proc logistic data=mydata ;*Full model for the outcome. Gives coefficient
parameters that can be applied to estimate p of outcome in other datasets
where
participants may have different values on model variables;
class everHP(ref='0')/param=ref;
class race(ref='1')/param=ref;
class momed(ref='1')/param=ref;
class sex smokes alcocat cdcBMI95 kc404 ;
model h_tri= everHP bmi8 avgsleephr pctfat pctcho fatratio alcocat
cpm13
ssb13_new bmic8 cdcBMI95 smokes sex race agechol momed depression bwt
bestgest momagedel kc404; *obtains model effect estimate;

```

```

weight SCW;

score data=mydata0 out=predy0; * Estimates the probability of outcome=1 for
each subject where everybody was set to E-, and the mediators too the original
values;

score data=mydata1 out=predy1; * Estimates the probability of outcome=1 for
each subject where everybody was set to E+ and the mediators took their
original values;

run;

data predy0; *Renames probability of outcome =1 among all arbitrarily set to
E- as PY0;
set predy0;
py0=P_1;
run;

data predy1; *Renames probability of outcome =1 among all arbitrarily set to
E+ as PY1;
set predy1;
py1=P_1;
run;

data mydataaw;
merge preda predy0 predy1 mydata;
run;

data mydataaw;
set mydataaw;
w= everHP/pa1 +(1-everHP)/(1-pa1);

```

```

run;

proc reg data=mydataw;
where everHP=0; *It averages this among only the unexposed so they have the
mediator as they have it when they are unexposed, but averages the outcome
they would had,
had they instead been exposed;
model py1=;
weight w;
run;

*Counterfactual 2= P (Ya*Ma*=1/cov) (2);

proc logistic data=mydata ;
model everhp= ;
score data=mydata out=predunca;

run;

data predunca;
set predunca;
Pa0=P_0; *P_0 stays there=unconditional probability of being unexposed;
run;

proc logistic data=mydata;
class everHP(ref='0')/param=ref;

```

```

class race(ref='1')/param=ref;
class momed(ref='1')/param=ref;
class sex kc404 ;
model everhp= race sex agechol momed depression bwt bestgest momagedel
kc404;
score data=mydata out=preda;

run;

data predal;
set predal;
Pa0cov=P_0;* Conditional probability of being unexposed;
run;

*ssb13_new avgsleephr smokes bmich cdcBMI95;
*avgsleephr everHP*avgsleephr pctfat pctcho plausiblerep fatratio alcocat
everhp*alcocat smokes cpm13
ssb13_new fg13kcal fg3100 bmich cdcBMI95;

proc logistic data=mydata ;
class everHP(ref='0')/param=ref;
class race(ref='1')/param=ref;
class momed(ref='1')/param=ref;
class sex smokes alcocat kc404 cdcBMI95 ;

model h_tri= everHP bmi8 bmi8 avgsleephr pctfat pctcho fatratio alcocat
cpm13
ssb13_new bmich cdcBMI95 smokes sex race agechol momed depression bwt

```



```

bestgest momagedel kc404;

weight SCW;

score data=mydata out=predy_;

run;

data predy_;
set predy_;
py=P_1; *Probability of outcome=1 given the exposure and mediator status they
actually have;

run;

data mydataw1;
merge preda predunca predy_ mydata;

run;

data mydataw1;
set mydataw1;

w1=Pa0/Pa0Cov;

run;

proc reg data=mydataw1;
where everHP=0;
model py=; *Probability of outcome=1 among the unexposed with the mediators
taking the values that they actually have;
weight w1;

```

```

run;

*Counterfactual 3= P YaMa=1|cov) (3);

proc logistic data=mydata;
model everhp= ;
score data=mydata out=predunca;

run;

data predunca;
set predunca;
Pa1=P_1; *P_1 stays there. Unconditional Probability of being exposed;

run;

proc logistic data=mydata;
class everHP(ref='0')/param=ref;
class race(ref='1')/param=ref;
class momed(ref='1')/param=ref;
class sex kc404 ;

model everhp= sex race agechol momed depression bwt bestgest momagedel
kc404;
score data=mydata out=preda;

run;

```

```

data preda;

set preda;

Palcov=P_1;*Conditional Probability of being exposed;

run;

data mydataw2;

merge preda predunca predy_ mydata;

run;

data mydataw2;

set mydataw2;

w2=Pal/PalCov;

run;

proc reg data=mydataw2;

where everHP=1;

model py=;

weight w2;

run;

```

Chapter 4:

Cardiovascular and Type 2 Diabetes Risk in Children with Externalizing Behavior Problems: A Systematic Review of the Evidence

Abstract

Externalizing disorders are the most common mental health diagnoses in children and adolescents, but despite their well-known association with obesity, it is unclear whether externalizing disorders and symptomatology are also risk factors for cardiovascular diseases (CVD) and type 2 diabetes mellitus (T2DM). Other common mental health problems, including depression and anxiety, are now established risk factors for these diseases. A systematic review was conducted following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to summarize and assess consistency in the literature of the association of childhood and adolescence externalizing problems/disorders with increased CVD/T2DM risk. I assessed the literature for evidence on the developmental timing at which increased risk becomes evident (childhood, adolescence, young-, mid- adulthood, later in life), and for evidence that the relationship is independent of body adiposity. Studies were graded for quality of evidence. Results: Findings supported a positive association of externalizing problems with T2DM and insulin resistance (100 % of 5 assessments), and with increased blood lipids (100 % of 4 assessments) among children and adolescents. Evidence was mixed and provided less support to the association with T2DM and blood lipids in adults (13% of 8 assessments) and among studies that assessed other outcomes in children or adults (69 % of 22 assessments). Studies in children were mostly cross-sectional and relied mainly on clinical assessments or on well-validated measures. Studies in adults were mostly prospective and used less valid assessment methods. Associations persisted in all 9 assessments in which models adjusted for BMI. Conclusions: Children with externalizing problems have increased CVD/T2DM risk that is already apparent before adolescence. These children may have increased CVD/T2DM risk regardless of body

adiposity. More studies are needed to examine effects after adolescence. Future studies must employ prospective designs, well-validated measures of externalizing behaviors, and only rely on objective assessments of T2DM and CVD. New research is warranted to identify the mechanisms that underlie these associations, especially those suitable to modification by intervention.

Introduction

Cardiovascular diseases (CVD) and Type 2 Diabetes Mellitus (T2DM) are major causes of morbidity and mortality, worldwide and in the US^{1,2}. These disorders and their biological precursors, once concentrated among older populations, are now increasingly diagnosed among the young³⁻⁵. Currently, only a fraction of CVD/T2DM can be explained by known risk factors and the identification of new ones, especially early-life risk factors, is a top priority in public health research^{3,6,7}.

Among adults, common internalizing mental health problems have recently been singled out as important contributors to the development and worsening of CVD/T2DM: depression, anxiety, and post-traumatic stress disorder (PTSD) are now, in fact, established risk factors for these diseases⁸⁻¹³. The role of externalizing psychopathology, on the other hand, has been investigated to a much lesser extent, which is surprising given the large body of research that supports associations, already evident in childhood, between Attention-deficit Hyperactivity Disorder (ADHD) and Conduct Disorder with obesity, itself a strong precursor of CVD/T2DM¹⁴⁻¹⁷. ADHD is the most commonly diagnosed behavioral disorder in the pediatric population, with approximately 10 percent of US children aged 3-17 years receiving a diagnosis, and as many as half of them displaying also additional behavioral or conduct problems¹⁸.

That obesity risk is already increased in children¹⁵ and adolescents with ADHD or Conduct Disorder makes externalizing psychopathology not only a plausible early life risk factor for CVD/T2DM, but also a relevant one for public health given the high prevalence of externalizing problems. The processes that lead to the development of cardiovascular disorders require many years to develop. Extensive evidence shows that early detection and intervention to stop these

processes can have an impact in reducing morbidity and mortality. Identifying the developmental timing of the emergence of CVD and diabetes risk in children with externalizing problems could therefore be critical for timely intervention.

Externalizing problems may be associated with CVD/T2DM through at least two pathways not involving increased body adiposity. First, persistent high levels of stress in psychopathology may disrupt the body's stress-response systems, the SNS-HPA (sympathetic nervous system and the hypothalamus-pituitary axis). Consequences to this disruption include a cascade of neurochemical and neuroendocrine modifications that over time could lead to chronic high levels of inflammation and high levels of insulin. Chronic high levels of inflammation induce increases in blood lipids¹⁹. Persistent high insulin would, in turn, also lead to development of insulin resistance, and high levels of insulin and glucocorticoids are known to be key contributors to atherogenic processes in coronary arteries²⁰. Second, externalizing psychopathology might influence CVD/T2DM through impulsiveness, low-inhibitory control, and low self-regulation. These symptoms have all been shown to associate with a myriad of unhealthy behaviors known to increase CVD/T2DM risk, at least in part, independently of body weight, including high-sugar content diets, high intake of sugar-sweetened beverages²¹, sleep disruption^{22,23}²⁴, physical inactivity, higher consumption of alcohol, and earlier initiation of tobacco smoking²⁵.

Identifying whether the association is substantively independent of body adiposity, through the pathways described above, would expand our understanding of the ways externalizing problems (and maybe mental health problems in general) get “under the skin” to cause physical disease. And in more practical terms, the finding could also provide new roadmaps for the formulation of interventions that ameliorate long-term consequences on physical health. By current clinical guidelines CVD/T2DM risk factors are assessed only among children/adolescents

with diagnosed overweight/obesity. If the relationship is only partially mediated by body adiposity then a sizable proportion of children with externalizing problems –those with body mass index within normal ranges- might be children with elevated, but unidentified and unaddressed, CVD/T2DM risk.

To my knowledge no prior attempts have been made at summarizing the extant literature on the topic. This systematic review summarizes and assesses the evidence from existing research for consistency with regards to three particular questions of interest:

- 1) Is there a positive association between externalizing behaviors/psychopathology, experienced during childhood and/or adolescence, and CVD/T2DM risk?
- 2) When, during the life course (childhood, adolescence, young adulthood, later in life) does increased risk become evident?
- 3) What is the evidence and the degree to which the relationship is independent of body adiposity?

Data was extracted from peer-reviewed articles with regards to study setting, study design, sample size, methods used for assessment of externalizing behaviors/disorders and CVD/T2DM, study findings, confounding control, and study advantages and limitations. In addition, a 0-5 point quality grade system was developed and applied to individually assess each of the studies included for propensity to bias.

Methods

This systematic review was conducted in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Ref).

Inclusion Criteria

In order to be included in this systematic review, studies were required to be original research reports of the association between an externalizing behavior problem/disorder, first experienced during childhood or adolescence, and an outcome indicating the presence of cardiovascular disease, T2DM, or indicating an elevated risk for those diseases. This relationship needed to be explicitly tested and reported by the study. Specifically, the study outcomes had to be one of: ischemic heart disease, coronary heart disease, stroke, hypertension, blood pressure, atherosclerosis, carotid-artery intima media thickness, total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, T2DM, insulin resistance, hyperglycemia, hyperinsulinemia, or endothelial function/dysfunction. Articles were required to be written in English and published within 1980-2018.

Exclusion criteria

Studies that met any of the following criteria were excluded from this review:

- Study based on a selected sample, i.e. excluded subjects with ADHD, excluded subjects with obesity and chronic diseases, sample was made entirely of subjects with bipolar disorder, etc.;

- Study relied on global measures of psycho-behavioral problems that do not discriminate externalizing from internalizing behavior problems;
- The unexposed group is made up exclusively of participants with other psychiatric diagnoses;
- Studies in which outcome was inflammation. Although inflammation is a major component of the development of CVD/T2DM, inflammation is not considered a specific marker of CVD/T2DM as it is present in a wide range of disorders unrelated to the cardiovascular and energy metabolism systems;
- The study outcome is a composite of chronic diseases that includes diseases unrelated to the cardiovascular or energy-metabolism systems or includes biomarkers known not to be causally associated with CVD or T2DM risk;
- Report does not present results adjusted for sex and age;
- Prospective studies that test whether CVD precursor or biomarker precedes the development of externalizing problems.

Search Strategy

Searches were conducted in two electronic databases, Pubmed/MEDLINE (Jan 9, 2019) and Web of Science (Feb 5, 2019). The search in Pubmed was built stepwise as follows: first, a list of search terms including medical subject headings and keywords associated with the concept of “externalizing behavior problems in children” was developed, that included: attention deficit and disruptive behavior disorder, child attention problems, child inattention, hyperactivity problems, attention deficit and hyperactivity problems, conduct disorder, child conduct problems, externalizing behavior problems, externalizing disorders, child behavior problems. These search

terms were grouped into a comprehensive “Exposure” search term using the Boolean operator (OR). Likewise, a list of medical subject headings designating cardiovascular diseases, T2DM, and their most common subclinical biological manifestations, was developed that included: cardiovascular diseases, hypertension, blood pressure, insulin resistance, hyperglycemia, hyperinsulinemia, type 2 diabetes mellitus, atherosclerosis, cholesterol, triglycerides. These search terms were also grouped using (OR) to create a comprehensive “Outcome” search term. The “Exposure” and “Outcome” search terms were then combined by (AND) to create the final term that was used to search for articles in Pubmed/MEDLINE. The search on Web of Science was conducted using the same search terms and the Topics option. Search results were limited to full-text articles, English language, and publication years between 1980 and 2018. Search terms are listed in Appendix Figure. A.4.1.

The searches on Pubmed/Medline and Web of Science retrieved n=1,383 and n=2,972 titles, respectively (Figure 4.1). Manual reviewing of these titles led to the selection of 91 articles, of which n=13 were duplicate titles and were discarded and to n=78 titles retained (53 titles from Pubmed/MEDLINE, and 25 titles from Web of Science searches). After excluding reviews, editorials, correspondence, and conference abstracts, a reading of the remaining abstracts -with application of inclusion and exclusion criteria- led to 43 abstracts being retained. Careful reading of the full-text articles associated to these selected abstracts –and again, applying inclusion and exclusion criteria- led to 18 articles being retained. In this step, n=10 articles were excluded because it was determined that the studies did not meet inclusion criteria: study outcome did not meet inclusion criteria (5), study did not assess externalizing problems in childhood or adolescence (1), study did not directly test the hypothesis of interest (2), article written in language other than English (2). Fifteen articles were excluded because it was determined studies met one or more

exclusion criteria: study based on a selected sample (8), study outcome was a composite score (2), study results were not minimally adjusted for age and sex (4), study did not discriminate externalizing problems from internalizing problems (1).

The reference lists of these 18 retained articles were screened for additional articles missed by Pubmed/MEDLINE and Web of Science searches, leading to the identification of 2 additional articles. Both these articles passed inclusion/exclusion criteria and were therefore selected leading to a final set of n=20 articles to be included in this systematic review.

Data extraction

From each reviewed article the following data was extracted author's name and year of publication, study design (prospective / cross-sectional), study setting (target population, sample selection: population-based, clinical sample, convenience sample), sample size, sex composition, ages at assessment of exposure and of outcome, method for assessment of exposure (diagnostic interview/ parent-teacher questionnaire/ self-reported), the exposure variable, method for assessment of outcome (objectively measured / clinical records / self-reported), the outcome variable, results (measures of association and corresponding standard deviation or 95% confidence intervals, when available; p-values otherwise), stratification or matching procedures, control for confounding (detailing variables when available), and study specific advantages and disadvantages.

The information extracted was organized into tables 4.2a and 4.2b, where articles appear indexed by study design, and sample size.

Evidence quality grade

The quality of the evidence provided by each of the studies reviewed was evaluated based on the following system: one point was given for each of: 1) Prospective design (versus cross-sectional); 2) Sample size > 500; 3) Assessment of externalizing problems based on diagnostic interview or by a screening tool with probed construct validity against DSM-IV/V criteria or the Achenbach's Child Behavior Check List; 4) Assessment of outcome by physician-made diagnosis, electronic search for physician-made diagnosis recorded in insurance or registrar databases²⁶ or by manual review of clinical records²⁷ (versus self reported); and 5) Control for confounding beyond age and sex.

Consistency of findings

Measures of association were classified as indicating elevated (or reduced) risk among the exposed if these associations reached statistical significance at 5 % confidence level (Tables 4.1a. and 4.1b.). Measures of association can however be valid but imprecise. Small but otherwise sound studies can produce valid effect estimates with confidence intervals that include the null. Arbitrarily characterizing such findings as supportive of the null hypothesis (no difference in risk between exposed and unexposed) may lead to erroneous conclusions in assessments of consistency of findings across studies. Accordingly, consistency of findings is assessed among statistically significant findings, but additional tables (Appendix tables A.4.1a. and A.4.1b) were constructed to show how consistency changes when non-statistical significant findings from valid studies are also considered as supporting elevated risk based on reported effect sizes (within range of effect sizes of statistical significant findings from other studies).

Results

Altogether, the 20 reviewed articles (Tables 4.1a and 4.1b) reported on 40 assessments of the relationship between some measure of an externalizing behavior problem/disorder, assessed during childhood or adolescence, and one of 10 different endpoints: T2DM or insulin resistance – indicated by HOMA-IR index- (12 associations examined ^{4,28-34}), blood pressure (14 associations examined ^{28,29,31,33,35-40}), subclinical atherosclerosis (3 associations examined ^{35,41}), CVD (1 association ⁴² reported), death from CVD (1 association reported ⁴³), endothelial function (3 associations reported ⁴⁴⁻⁴⁶), unspecified dyslipidemia (1 association reported ²⁹), total cholesterol (3 associations reported ^{28,33}), LDL-cholesterol (1 association reported ³³), and triglycerides (1 association reported ³³).

Twelve ^{4,28-30,33,35-37,41-44,47} of the 20 articles reported on prospective studies, 7 ^{33,34,37-39,45} reported studies that used cross-sectional designs, and 1 article³³ reported on a study that used both prospective and cross-sectional designs. The latter is considered in this review either a prospective or a cross-sectional study, as it pertains to its different analyses and reports. Overall, 30 of the 43 associations reported by these 20 articles were assessed using a prospective design.

All but one⁴² of the prospective studies were conducted with population-based samples from the US, and 6 other countries. The other study⁴² was conducted with a clinical sample in the US. The sample sizes of prospective studies varied from n=89³⁶ to n=107,847²⁹ and the average evidence quality grade (G) among these studies was 3.7, range= 2 to 5. The length of study follow-up period varied within a range of 3-50 years (mean= 22 years). Three^{4,36,42} of these studies were conducted in male-only, and one in a female-only sample.

Six of the 9 cross-sectional studies were conducted in population-based samples from the US and 4 other countries. The other 2 cross-sectional studies were conducted in clinical samples

from the US. Sample size varied across these studies, from n=60 to n=25,812. The average evidence quality grade was 3.6, range= 2 to 5. One of these studies was conducted in a female-only⁴⁶, and one study was conducted in a male-only sample³⁹.

Two of the studies^{32 40} included in this review, are studies that examined the association of an externalizing disorder with a cardiovascular risk factor (or T2DM) with the hypothesis that the relationship operates in the direction opposite to that hypothesized in this review. Specifically, these studies examined whether hypertension⁴⁰ or T2DM³² are risk factors –as opposed to outcomes- of ADHD. Both these studies used cross-sectional designs and used odds ratios as measures of association. Because $OR_{outcome} = OR_{exposure}$, the odds ratio of ADHD between those with- and those without hypertension (or T2DM) reported by these studies can likewise be interpreted as the odds ratio of hypertension (or T2DM) between those with ADHD and those without ADHD and these studies were thus considered suitable for inclusion in this review. Two of the articles included in this review examined the relationship between “self-control” in childhood with incident T2DM³⁰ or coronary artery calcification⁴¹ in adulthood, both using data from the Cardiovascular Risk in Young Finns study, and hypothesizing that high self-control would have a protective effect. Their measure of self-control –a dimensional score- was derived by adding-up reverse coded questions on hyperactivity and aggressive behavior. Their research can therefore be seen as examining the protective cardiovascular effects of low externalizing problems which, while admittedly not the exact same question that this review investigates, could nonetheless provide valid and important evidence if the relationship were one that operated over the full dimension of externalizing symptomatology.

Studies that examined T2DM or insulin resistance

Eight studies examined T2DM or HOMA-IR as endpoints, altogether assessing 12 relationships. Of these assessments, 6 (50%) found positive^{28,29,32-34} and 6 reported no associations^{4,28,30,31}. Of the 6 positive associations, 2^{28,29} were observed by studies using a prospective design, while all 6 findings of no association were reported by prospective studies. Five of the 12 assessments, one prospective and 4 cross-sectional, were conducted among children or adolescents and all five of them found positive associations. Only 1 of the 7 studies that assessed outcomes in adulthood found a positive association. However, another 3^{4,28} of those assessments in adults reported effect estimates consistent with a positive association (OR: 0.6 (95% CI=0.3,1.7) (attention)²⁸, OR: 1.2 (95% CI=0.5,3.0) (hyperactivity)⁴, OR: 1.4 (95% CI=0.5,4.4) (conduct problems)⁴) that did not reach statistical significance. Studies that found positive and statistically significant associations with T2DM risk reported association estimates in the 2.8-4.1 range^{28,29,32}, and those that noted positive associations with HOMA-IR reported effect sizes of about 0.25 unit increases in HOMA-IR per 1-sd increase in externalizing problems³⁴ or 0.30 unit increase in girls with CBCL-aggressive behavior vs. no aggressive behavior³³.

Overall the quality of evidence was slightly higher among studies that noted positive associations among children and adolescents (grade =3.6) than the one study that noted a positive association in adults (grade =3.0), or those that noted no associations among adults (grade =3.3). The study²⁹ with the best evidence grade (grade=5), a large longitudinal population-based study of adolescents found an association of ADHD diagnosis with incident T2DM 3 years later, HR= 2.8 (95% CI=2.0, 4.1). In general, studies that reported positive associations used more valid methods for assessment of externalizing problems/disorders. Two^{29,32} of the 6 positive associations were observed in studies that relied on physician-diagnosed ADHD and the 4 other were observed in studies that employed widely-used screening instruments shown to be reliable and valid across

different populations and to be consistent with current clinical criteria for diagnosis of ADHD and CD (Achenbach Child Behavior Checklist (CBCL)³³ and the Behavior assessment system for children, 2nd edition (BASC-2)³⁴), or by psychologists' direct observation of the children²⁸. On the other hand, none of the studies that found no association relied either on clinical diagnoses or any screening tools. They relied instead on the now-outdated Rutter's scales^{4,31} –a questionnaire developed in the 1960's that is less consistent with current clinical diagnostic criteria- or on a study-developed measure of high self-control without published evidence of construct validity³⁰ and no evidence of comparability with other more widely-used valid measures.

Studies that found positive associations were also more likely to have relied on objective assessments of outcomes. All 6 positive associations were observed in studies that relied either on physician-diagnosed T2DM^{29,32} or on assessments of HOMA-IR^{33,34}. On the other hand, 3^{28,31} of the 6 findings of no association were reported by studies that relied on self-reported T2DM, and by a fourth study that relied, at least partially, on self-reported T2DM³⁰. Studies reporting positive or no-associations with T2DM or HOMA-IR did not clearly differ with regards to sample size or confounding control. No discernible trend was seen of particular subdomains of externalizing psychopathology being more likely than others to be associated with T2DM or HOMA-IR.

Although the number of studies is too small to make any conclusive assessments, evidence hints that the associations with T2DM or IR might be stronger among girls/women. A study²⁸ that investigated the relationship of childhood distress proneness with adult T2DM assessing the relationship only among women (not enough diabetes cases arose among the study men) found a strong positive association (OR=4.1, 95% CI=1.2, 13.7). In another study³³, aggressive behavior at age 14 was cross-sectionally associated with higher HOMA-IR among girls only.

Studies that examined blood pressure

Ten studies investigated blood pressure-related endpoints^{28,29,31,33,35-39}, altogether examining 14 relationships with: SBP or DBP values (10), Stage II hypertension defined as SBP ≥ 160 mmHg, and DBP ≥ 100 mmHg (2), or self-reported hypertension (2). Four^{28,29,37,39} of these 14 assessments reported positive associations, 3^{33,40} reported inverse associations, 1³⁵ assessment found the association to be positive among women and inverse among men, and the other 6^{28,31,36-38} assessments found no association. Of these 14 analyses, 10 were examined by prospective designs^{28,29,31,33,35-37}. Positive, inverse, and no associations were reported in similar fashion by prospective and cross-sectional studies.

Studies that noted positive associations with blood pressure reported a wide range of effect sizes: a 1-sd increase in distress proneness at age 7 was associated with a 7-point increase in SBP at age 42²⁸, but in another study the highest score of hyperactivity in childhood, versus no hyperactivity, was associated with only 0.4 point increase in SBP at ages 24-30 (among women only)³⁵. In studies that examined clinically diagnosed hypertension, ORs varied from 1.13²⁹ to 4.89³⁹, with the smaller effects found for ADHD²⁹ and hyperactivity²⁹ and larger effect sizes found for overweight/obese children with family history of hypertension and high Diagnostic Interview Schedule for Children (DISC) -delinquent scores³⁹.

Three^{33,35} of the 4^{33,35,40} findings of inverse associations of externalizing problems with blood pressure were observed among boys or men, and the effect sizes were very small for ADHD (OR=0.97, (95% CI=0.96, 0.99)⁴⁰ and hyperactivity (beta coefficient for SBP: -0.11, p=0.04)³⁵, and higher for boys with consistent high CBCL-aggressive scores throughout childhood (2.8 points reduction in DBP by age 14, Beta $\text{aggressive score} \times \text{age}$: -0.02 (95% CI=-0.036, -0.004)³³.

The quality of evidence from studies that observed positive (grade=3.8) or inverse associations (grade=4.0) was better than that from studies that did not find associations (grade=3.3). Studies that observed positive and inverse associations with blood pressure were more likely to have used a more valid method for assessment of externalizing problems. Physician diagnosis of ADHD²⁹, psychologist direct observation of children²⁸, or any of the well-validated Achenbach scales (CBCL or Teacher's Report Form (TRF)³⁹) were used in 3 of 5 findings of positive associations, in 3^{33,35,40} of the 4 findings of inverse associations, but in none of the findings of no association.

No evident differences were found with regards to the quality of assessment of blood pressure across studies and no apparent differences were noted across studies that observed positive, inverse, or no associations with regards to sample size, except that all the very small studies (sample sizes < 200) found either positive or no associations, whereas all studies that reported inverse associations used samples with $n > 1,000$.

Studies that examined blood lipids

Three independent studies examined blood lipids, altogether assessing 6 associations with different endpoints: dyslipidemia (1²⁹), triglycerides (1³³), LDL-Chol (1³³), and total-Chol (3^{28,33}). Four of these assessments found positive and statistically significant associations with blood lipids (all 4 in children or adolescents)^{29,33} and the other two (in adults)²⁸ found positive associations with similar effect size that did not reach statistical significance. Four of 6 positive associations were observed only among boys³³ or men²⁸. Dyslipidemia at mean age 18 was associated with ADHD at age 13 (OR=2.1, $p < 0.001$)²⁹, with no reported sex differences. In a cross sectional study³³ of 14 year olds, each 1-point increase in TRF-aggressive behavior score (range 0-40) was

associated with increased total-Chol (Beta: 0.018, 95% CI= 0.003, 0.0320) in boys only, LDL-Chol (Beta: 0.015, 95% CI= 0.002, 0.027) in boys only, and with triglycerides (Beta: 0.011, 95% CI= 0.002, 0.020) in boys and in girls (Beta: 0.013, 95% CI= 0.001, 0.025). In a prospective study a 1-sd increase in attention scores at age 7 was associated with a non-statistically significant reduction of 5 mg/dl of total-Chol at age 42 among men only (small size, n= 158), and a 1-sd increase in distress proneness score predicted a 5 mg/dl non-statistically significant increase in T-Chol, also among men only²⁸. Overall, the quality of evidence from these studies that examined blood lipids was slightly higher (grade=4.2) than the average quality for all studies (grade=3.6).

Studies that examined other outcomes

Together, the articles reviewed assessed 8 associations between some externalizing problem and one of subclinical atherosclerosis, CVD, or endothelial function, but the number of studies per endpoint is very small for reliable inferences to be drawn about any specific outcome. Four of the 8 assessments found positive associations, 2 found no associations, and 2 found inverse associations.

The relationship between childhood externalizing problems with subclinical atherosclerosis endpoints in adulthood was examined by 2 studies, both using data from the Cardiovascular Risk in Young Finns study, a 32-year follow-up study, together examining 3 different relationships. One of the studies³⁵ noted a positive association of mid-adulthood c-IMT with childhood hyperactivity, an association that was observed only among women. Women in the top tertile for childhood hyperactivity showed, on average, an increase of 0.03 mm in c-IMT when compared with women in the bottom tertile, an increase that according to the study authors could signify a 15% to 20% increase in subsequent CVD risk. In the same study, “negative emotionality”,

assessed by a study-developed measure of aggressive-type behavior was not associated with c-IMT. In the other study⁴¹, a 1 standard deviation increase in “self-control” was inversely and moderately associated with the presence of coronary artery calcification (OR= 0.59, CI= 0.38, 0.92), a finding which could be seen also as showing a positive association of moderate size between low self-control (an externalizing problem) and coronary artery calcification.

The association of externalizing problems with CVD endpoints was examined by 2 studies. In a long follow-up study with a large sample⁴³, childhood conduct problems were positively associated with a small increase in risk (RR= 1.17, 95% CI= 1.04, 1.32),) of death from CVD by age 65 in men and with a smaller association in women (RR=1.10, 95% CI= 0.92, 1.32). In the other study,⁴² conducted with a very small clinical sample (n=271), no association was observed (OR=1.01) between physician-diagnosed childhood ADHD and self-reported CVD 32 years later.

Three studies examined endothelial function. Two used data from a study of school children in Sweden. Using a cross-sectional design, one of these studies⁴⁵ reported an association of higher disruptive behavior score with better –not worse- endothelial function at age 14, among boys only. The other study⁴⁴ found a prospective association of higher disruptive behavior score at age 14 with worsening endothelial function between ages 14 and 17, also observed only among the boys. The third study that examined endothelial function⁴⁶ was a very small (n=60) cross-sectional study in a clinical sample of 15-year old girls. In the study, girls with Conduct Disorder appeared to have better endothelial function than control girls. But the quality of evidence of this study was low given the small sample size and methodological limitations including no control for confounding besides age and sex.

The role of body adiposity in mediating the main associations

In all, these articles assessed 40 relationships, finding 22 positive associations. None of the studies reviewed conducted any formal assessments of mediation by BMI. Of the 22 reported positive associations, 9 had been adjusted for BMI in multiple regression analyses, suggesting that the relationships assessed might be at least partially independent of BMI. The remaining 13 associations were not adjusted for BMI and therefore it is not known whether they too might, to any extent, be independent of BMI. One study reported a positive cross-sectional association, apparent among girls only, of CBCL-aggressive behavior score with increased HOMA-IR at age 14 y: among these girls each 1-point increase in the score for aggressive behavior –the score range was 36- was associated with a 1% increase in HOMA-IR index. Following simultaneous adjustment for BMI and smoking led to a reduction in the size of the association by 60 %.

Developmental timing of the association of externalizing problems with CVD/T2DM risk

Among the studies reviewed, positive associations with T2DM or HOMA-IR were observed in children as young as age 9. No studies examined these endpoints at younger ages. No study assessed diabetes or HOMA-IR on more than just one occasion. Positive associations were observed by all 5 studies that examined T2DM or HOMA-IR in children or adolescents, however, results from studies that tracked participants until adulthood were much less consistent, likely due to the fact they tended to rely on less valid and less reliable measures of externalizing problems. Not surprisingly, these studies among adults were too more likely to report imprecise estimates of association. Evidence from the studies that found positive associations among adults (statistically significant and non-statistically significant) were of better quality than those that did not (grade=3.7 vs. grade=3.0).

Overall, the best quality studies found positive associations with T2DM or HOMA-IR from late childhood up until mid-adulthood. Childhood externalizing problems were found to be positively associated with T2DM or HOMA-IR at ages 9³², 10³⁴, 14³³, 18²⁹, and 42²⁸.

Blood pressure related endpoints were examined by these studies in children as young as age 8³⁹. Three studies that assessed blood pressure before age 15 found inverse small associations^{33,40} and two found no association^{36,38}. Among studies that assessed blood pressure in young and mid-adulthood, the 2 studies that examined the relationship with childhood attention/inattention found no association^{28,37}, but all 4 studies that examined hyperactivity or aggressive behaviors found positive associations with SBP (mmHg) at ages 24-30³⁵ and 42²⁸ years, and with diagnosed HTN at ages 18²⁹ and 29³⁷ years. It is unclear from the studies reviewed whether the inverse association with blood pressure observed (mostly among boys) before age 15 is one that persists into later developmental stages for at least some individuals.

The association of externalizing problems with blood lipids was examined and was found to be positive at ages 14³³, 18²⁹ and 42²⁸. None of the studies evaluated blood lipids before age 14. Endothelial function was only assessed during adolescence and the best quality evidence showed a positive (worsening function) association⁴⁴. Subclinical atherosclerosis was assessed only in mid-adulthood where 2^{35,41} of 3 assessments revealed positive associations.

Discussion

This systematic review summarized and evaluated the consistency in the existing literature on the relationship of externalizing problems/disorders experienced in childhood and adolescence with CVD/T2DM risk. The developmental period at which the associations become observable,

whether they persist into adulthood, and whether they are independent of the already known positive association of externalizing problems with body adiposity, were additional questions of interest.

Overall, and despite great methodological heterogeneity among studies, this review found consistent evidence of a positive association between externalizing problems with increased risk for CVD and T2DM. Although several studies found no evidence of associations, studies that used more valid methods consistently did. Current evidence is particularly solid for associations with T2DM risk (particularly among children/adolescents, and stronger among girls and women) and blood lipids (stronger among boys/men). Based on more limited evidence, the studies also support relationships with subclinical atherosclerosis and worsening endothelial function. Associations were found for clinical diagnosis of ADHD as well as for subclinical and dimensional measures of aggressive behavior, conduct problems, hyperactivity and impulsivity, low self-control, and low attention symptomatology.

This review also found evidence that these associations emerge as early as late childhood, and they are evident by mid-adolescence for a wide range of CVD/T2DM related endpoints: T2DM, HOMA-IR, endothelial function, total-Chol, LDL-Chol, and triglycerides. We also found that externalizing problems are likely not associated with increased blood pressure until late adolescence or mid-adulthood, and that high blood pressure might result from hyperactivity and conduct problems but not from attention problems.

Evidence also suggests that the positive associations with CVD/T2DM operate in part independently of BMI. Although adjusting regression models for BMI would not be appropriate to assess mediation in the presence of exposure-mediator interactions and none of the studies

showed evidence that such interactions were not present, the fact that associations persisted in 8 of the 9 instances in which BMI was adjusted for, indicates that some proportion of the associations operate through mechanisms not involving BMI. As total and adjusted effect sizes were not separately reported in these studies it is not possible to approximate (even informally) the relative magnitude of this direct effect not mediated by BMI.

Stress-related psychopathology, including externalizing psychopathology, is thought to influence CVD/T2DM risk through SNS/HPA-mediated neuroendocrine effects and/or by its association with unhealthy behaviors. Sustained stress experienced during particularly sensitive developmental periods could be especially deleterious^{48,49}. The nervous, endocrine, and immune systems undergo critical maturation throughout childhood⁵⁰ and it is possible that stress-related psychopathology in early life could act as a modifying factor in the maturation process of these systems becoming embedded in a lasting fashion, with long life effects and vulnerability to chronic disease. Poor health behaviors known to influence CVD/T2DM are also known to be established before adulthood and to be stubborn to later modification.

The precise nature of the mechanisms involved in mediating the effects of externalizing problems on CVD/T2DM risk -as well as the relative contribution by different mechanisms- might not be constant over the life-course due to the existence of sensitive developmental periods and/or due to changes in the exposure to unfavorable health behaviors throughout developmental stages. For instance, high intake of sugar-sweetened beverages might be a key mediator in childhood, but smoking may be a more important one in late adolescence. The relative importance of pathways may also vary across populations with different prevalence of obesity, smoking, and other health behaviors.

Unlike internalizing problems (including depression and anxiety) which have been consistently linked to an overactive SNS-HPA axis, externalizing problems have also been associated with sympathetic underarousal, with lower basal cortisol, and blunted cortisol response^{51,52}. Hypocortisolism is, in turn, associated with decreased heart rate and hypotension. This observation would be at odds with the model described above to explain positive effects on CVD/T2DM risk, but it would provide a basis for the small inverse association of externalizing measures with lower blood pressure in children observed by a couple of methodological sound studies in this review. It has been observed that sympathetic underarousal and low cortisol profiles are specifically observed among more delinquent or severe cases of conduct disorder⁵², less so in community samples⁵¹. Indeed, in this review, an inverse association with blood pressure was reported for children with aggressive behavior scores consistently above the 95th percentile throughout childhood and adolescence versus children with low score³³. In community samples, however, children with comorbid anxiety and conduct problems were shown to have higher –not suppressed- levels of cortisol⁵¹. Internalizing-externalizing comorbidity is highly prevalent so community-based studies might find different results regarding blood pressure depending on the prevalence of externalizing-internalizing comorbidity and on whether studies recruited and retained participants with more severe behavior problems. None of the studies included in this review examined SNA/HPA activation/attenuation effects in relationship to externalizing (or internalizing) behavior problems.

Limitations

This systematic review has some limitations. First, overall, the literature on childhood externalizing problems and CVD/T2DM is small and is heavily focused on diabetes and blood pressure. Few articles investigated other clinically relevant outcomes including blood lipids, atherosclerosis, and endothelial function. I searched two of the most comprehensive electronic databases, but it is still possible that coverage of the existing literature by these databases was not complete and therefore that some relevant articles were missed. Second, a second reviewer was not used in the literature search process and it is possible that the final list of articles would have been slightly different had there been one additional reviewer.

Third, articles were chosen for inclusion based on whether they examined one (or more) of a pre-defined set of CVD/T2DM-related outcomes known to be causally associated with heart disease, stroke, and T2DM, and considered relevant to CVD/T2DM risk in clinical practice. This list was not exhaustive, however, with regards to all biological parameters known to relate with the functioning of the cardiovascular and metabolic systems and therefore research that examined relationships with such outcomes not currently employed in the risk screening in clinical practice not was not covered by this review (i.e. resting heart rate). Lastly, only-English written articles were included, and it is possible that results would have been somehow different without this restriction.

Recommendations

The current literature is both scarce and limited by a range of methodological shortcomings. Future studies should strictly rely on the use of well-validated measures of externalizing symptomatology or diagnoses, objective assessments of CVD/T2DM risk, and

employ prospective designs, ideally - in particular for studies with short follow up - relying on both baseline and end-of-study assessments of study outcomes.

The use of multiple informants of externalizing behavior has been shown to increase validity of assessments, and external informants –as opposed to self- are known to be particularly more valid for assessment of externalizing psychopathology⁵³. Only a few of the reviewed studies relied on more than one informant but those that did, and especially those that included reports from parents and teachers were more likely to observe positive associations.

The assessment of CVD/T2DM risk among children is currently handicapped by the fact that normative data has not yet been established for this age population making it difficult to evaluate the clinical significance for CVD/T2DM risk of small increments in the values of parameters such as HOMA-IR, blood lipids, and blood pressure. Furthermore, studies in this review that assessed peripheral endothelial function among adolescents by measuring a reactive hyperemia index relied on algorithms developed for adult populations and it is unclear how findings would differ with more age-appropriate assessments.

Control for confounding was in general insufficient and few studies adjusted for factors other than basic demographics. Family history of psychiatric diseases – including maternal depression -, diabetes, and cardiovascular disorders are all associated with externalizing psychopathology and with CVD risk therefore failing to adjust for these factors may likely bias effect sizes against the null. Pregnancy and birth outcomes are additional likely confounders not accounted for in any of the studies reviewed. Common genetic and/or neurobiological vulnerabilities could, in addition, be an alternative explanation for the relationships examined in this review but no research has investigated these pathways yet.

Phenotypic distinctions within externalizing psychopathology, such as inattention, hyperactivity, impulsivity, and aggression, may have critical bearings on risk for certain outcomes or might have unique developmental sensitive points but very few studies examined these subdomains separately. The very few that did suggested not only that these differences may indeed exist but showed, in addition, that these differences may also interact with sex. Relatedly, internalizing and externalizing comorbidity is another aspect that studies should consider given the conflicting evidence on the roles of externalizing and internalizing psychopathology in activation/attenuation of the SNP/HPA axis and also in their possibly differing relationships with health behaviors and coping mechanisms throughout developmental stages and across the sexes. For example, while externalizing behaviors in childhood are associated with earlier initiation of smoking, withdrawal and anxiety are associated with delayed initiation. Two of the studies included in this review also examined the role internalizing problems and their results support opposite conclusions. In one of them, a cross-sectional assessment³⁴ of children aged 9-12y, BASC-2 externalizing problems (but not BASC-2 internalizing problems) were associated with higher HOMA-IR. But, in a very small study⁴⁶ of 15-year old girls, n=60, girls with “Conduct Disorder only” had better endothelial function than did girls with “Conduct Disorder + anxiety”.

Conclusions

This systematic review of the literature found evidence of a positive association between childhood and adolescence externalizing problems with increased risk for CVD and T2DM. Children with externalizing problems appear to have increased risk of developing T2DM, and to have unhealthy levels of blood lipids. Based on more limited evidence and mixed findings, they

might also have worse endothelial function and subclinical atherosclerosis. CVD and T2DM risk appear to be already elevated among children with externalizing problems before adolescence. The evidence suggests, in addition, that externalizing problems influence CVD/T2DM risk at least in part independently of their effect on BMI. These results show that long physical disease burden associated with externalizing psychopathology might be greater than thought, that strategies that target excess body weight may be insufficient to address physical health problems among these children, and that CVD/T2DM risk monitoring might need to be extended to non-obese children with externalizing problems. Much research is needed to confirm findings, including prospective studies in children and adolescents that employ well-validated measures for assessment of clinical and subclinical symptoms that distinguish hyperactive, inattentive, and other externalizing problem subtypes. Studies that can also account for internalizing/externalizing/sex interactions would be particularly informative and especially so if they examined differential associations with SNS/HPA axis disruption and with propensity to adoption of unhealthy/coping behaviors.

Figures and tables

Figure 4.1: Literature search flow-chart

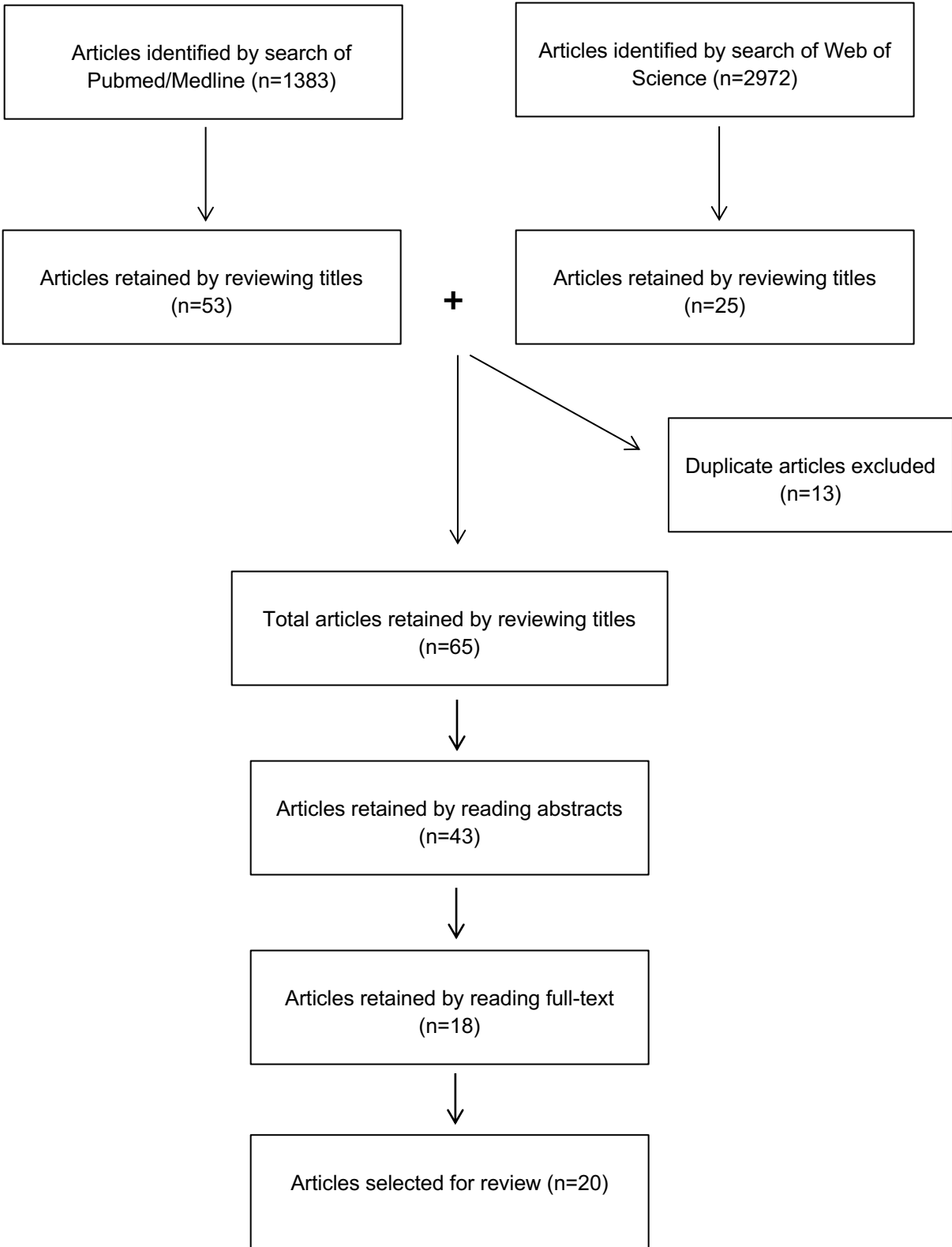


Table 4.1. a: Summary of all findings reported by studies in review, by study outcome

Outcome	Associations with the outcome tested		Risk of outcome was elevated among the exposed*		Risk of outcome was the same among exposed and unexposed		Risk of outcome was reduced among the exposed*	
	N	Average G	% (n/N)	Average G	% (n/N)	Average G	% (n/N)	Average G
T2DM / HOMA-	12	3.4	60 (6/12)	3.5	40 (6/12)	3.3	--	--
IR								
Blood pressure	14	3.6	36 (5/14)	3.8	43 (6/14)	3.3	21 (3/14)	4.0
Subclinical atherosclerosis	3	3.3	67 (2/3)	3.0	33 (1/3)	4.0	--	--
Endothelial function	3	3.3	33 (1/3)	4.0	--	--	67 (2/3)	3.0
Blood lipids	6	4.2	67 (4/6)	4.3	33 (2/6)	4.0	--	--

G= Evidence quality grade (range 0-5)

*Associations are statistically significant

Table 4.1. b: Summary of study findings, by timing of outcome assessment (childhood/adolescence or adulthood) and by study outcome

Outcome	Associations with the outcome tested		Risk of outcome was elevated among the exposed*		Risk of outcome was the same among exposed and unexposed		Risk of outcome was reduced among the exposed*	
	N	Average G	% (n/N)	Average G	% (n/N)	Average G	% (n/N)	Average G
Studies that assessed outcomes in childhood or adolescence								
T2DM / HOMA-IR	5	3.6	100 (5/5)	3.6	--	--	--	--
Blood pressure	7	3.6	29 (2/7)	4.0	29 (2/7)	2.5	43 (3/7)	4.0
Subclinical atherosclerosis	0	--	--	--	--	--	--	--
Endothelial function	3	3.3	33 (1/3)	4.0	--	--	67 (2/3)	3.0
Blood lipids	4	4.3	100 (4/4)	4.3	--	--	--	--
Studies that assessed outcomes in adulthood								

Table 4.1b Cont'd

T2DM / HOMA-	7	3.6	14 (1/7)	3.0	71 (6/7)	3.3	--	--
IR								
Blood pressure	7	3.7	43 (3/7)	4.0	57 (4/7)	3.5	--	--
Subclinical atherosclerosis	3	3.3	67 (2/3)	3.0	33 (1/3)	4.0	--	--
Endothelial function	0	--	--	--	--	--	--	--
Blood lipids	2	4	--	--	100 (2/2)	4.0	--	--

G= Evidence quality grade (range 0-5)

*Associations are statistically significant

Table 4.2. a: Studies that examine the association of childhood/adolescence externalizing behavior problems with CVD/T2DM risk/outcomes

Author (Year of publication)	Setting: Population-based/Clinical sample/Convenience sample	Sample size (analytical sample), Gender, Age at exposure assessment, Age at outcome assessment	Exposure assessment: Diagnostic interview/ Parent-Teacher questionnaire/ Self-reported	Exposure variables	Outcome assessment: Objectively measured/ Clinical records / Self-reported	Outcome variables	Results	Stratification/ Matching/ Confounding adjustment	Assoc. independent, or partially independent, of BMI	Advantages / Limitations	G
Prospective studies											

Table 4.2.a Cont'd

Chen, MH (2018) ²⁹	Population based: Adolescents and young adults in the Taiwan National Health Insurance Plan (covers 99% of Taiwan's population) w/o mental health or T2DM	N=107, 847, 79% M, Mean age 13y range 10-29y, Mean age at diagnosis: 18y	Insurance records of diagnosis of ADHD based on interview by board-certified psychiatrist occurring 2002-2009.	ADHD diagnosis on insurance records (Yes, No)	Records of physician-diagnosed T2DM, based on laboratory examination, occurring between diagnosis of ADHD and end of 2011 or death. Records of hypertension and dyslipidemia (unspecified, incident or prevalent)	Main outcome: First diagnosis of T2DM. Secondary outcomes: Prevalent or incident diagnosis of hypertension or dyslipidemia	In multivariate Cox regression analysis, a diagnosis of ADHD was associated with incident T2DM, (AHR: 2.84, 95% CI= 2.03-3.97) in full sample, and also among adolescents: (AHR: 2.83, 95% CI= 1.96-4.09). In Chi-Square tests, ADHD associated with hypertension (OR=1.13	Exposed and unexposed matched on age, sex, and time of enrollment. Models were adjusted for age, sex, urbanization, and	Association was independent of obesity	Prospective design, very large sample, uses gold-standard assessment of exposure and outcome / Possible bias due to passive ascertainment of exposure and outcome if	5
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Table 4.2.a Cont'd

	diagnoses						p<0.001) and with diagnosed dyslipidemia (OR=2.07 p<0.001)	income, use of ADHD medications, and medical comorbidities considered by authors to be confounders: hypertension, dyslipidemia, and obesity		participants with ADHD were more likely to receive a posterior diagnosis of diabetes simply by seeing health care professionals more often. Also, some likely residual confounding, and possibly,
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Table 4.2.a Cont'd

										bias due to over-adjustment for sex, and age (matching variables and also confounders in prospective study)	
Von Stumm, S (2011) ³¹	Population based: The Aberdeen Children of the 1950s study,	N=7,183, 49%M, Age 6-12 y, Age 46-51 y.	Teacher version of the 26-item Rutter Scale B.	Hyperactivity and conduct problems domains were identified by	Participants self-reported on physician-diagnosed medical conditions	Diabetes (Yes, No) and High blood pressure (Yes, No)	No association found of hyperactivity (AOR= 1.01, 0.89-1.15) or conduct problems (AOR=1.06,	Age, intelligence at age 11, social class or origin, and	NA	Prospective design with long follow-up, large population based sample	3

Table 4.2.a Cont'd

	<p>from the Aberdeen Area, Scotland, UK</p>			<p>factor analysis of teacher's reports. Score values on each domain were standardized for analysis</p>			<p>0.95-1.20) with high blood pressure, or of hyperactivity (AOR=1.06, 0.77-1.46) or of conduct problems (AOR=1.04, 0.79-1.38) with diabetes among men. No association found of hyperactivity (AOR= 1.04, 0.89-1.22) or conduct problems (AOR=1.07,</p>	<p>educational attainment</p>		<p>/ Use of a now-somehow outdated questionnaire for assessment of behavior problems, outcome was self-reported, control for confounding was limited</p>
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Table 4.2.a Cont'd

							0.90-1.27) with high blood pressure, or of hyperactivity (AOR=1.11, 0.73-1.69) or of conduct problems (AOR=0.78, 0.43-1.43) with diabetes among women.				
Maughan, B (2014) ⁴³	Population based: the Medical Research Council's	N=4158, 52% M, ages 13 and/or 15 y,		7-item "Conduct Problems" factor was identified by Confirmatory	Underlying cause of death was ascertained from National Health Service Central Register	Time to the first of death from cardiovascular diseases,	In Cox proportional hazards models, conduct problems were associated with	Social class of origin, and participants	Not assessed	Prospective design with long follow-up, large and population	4

Table 4.2.a Cont'd

<p>National Survey of Health and Development birth cohort study: all births occurring within a 1-week in May 1946, in the UK, who survived to age 15y</p>	<p>age 65 y</p>		<p>Factor analysis. Total scores (sum of 7 items, range 0-14) were averaged if participants had assessments at age 13 and 15 yr. Scores were standardized .</p>		<p>emigration, or end of study at participant's age of 65</p>	<p>elevated relative risk of death from coronary heart disease in men (ARR=1.17, 1.04-1.32) and in women as well, but to a lesser degree (ARR=1.10, 0.92-1.32). <i>p</i>- for test of interaction between gender and conduct problems=0.5</p>	<p>cognitive ability, assessed at school at age 11 y</p>		<p>-based sample, outcome was objectively assessed / Use of an outdated measure of behavior problems,</p>
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Table 4.2.a Cont'd

Pulkki - Raback, L (2017)) ³⁰	Population based: Subjects in the Cardiovascular Risk in Young Finns Study who were free of Type-1 diabetes	N=3,553, 48%M, Ages 3-18 y, Ages 35-50 y	Main caregivers rated children with two study specific scales derived from the Health Examination Survey: 1-item "Physical self-control" scale, and a 6-item "Aggression control scale" with answers on a 5-point Likert scale. Scores from the two scales were	Self-control score	Participants were classified as having T2DM during follow-up if met anyone of: 1) Lab tests (Fasting plasma glucose levels ≥ 7 mmol/L at any follow-up visit 2001, '07, and '12, Hemoglobin A1c ≥ 48 mmol/mol at 2011 visit) 2)	T2DM (Yes, NO)	Self-control score was not associated with incident T2DM (ARR ₁ : 0.94, 95% CI: 0.78-1.13; ARR ₂ : 0.95, 95% CI: 0.79-1.13)	1Age, gender 2 Age, gender, childhood cardiovascular (insulin, LDL-Chol, HDL-Chol, Triglycerides, Sys-BP, BMI), and dietary risk	NA	Prospective design, large population based-sample, long follow-up, comprehensive adjustment for childhood CVD risk factors / Assessment of outcome includes	3
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Table 4.2.a Cont'd

			standardized and summed together into a "Self-control" score		A record of a physician's diagnosis in the National Social Insurance			factors (fruit, vegetables, meat, and fish consumption)		self-reported T2DM, use of study-developed measures of behavior problems not readily comparable with currently used standardized scales, a single item assessed
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Table 4.2.a Cont'd

										physical self-control.	
Goodwin, RD (2009) ⁴	Population based. Representative sample of all boys born in Finland in 1991: The "From Boy to Man" follow-up study included in the	N=2712, 100%M, Age 8y, Age 18-23y	Parents and Teachers completed respective versions of the validated 31-item Rutter's questionnaires for assessment of children's behavior problems, with individual items rated on a 3-point Likert scale	Parent's and teacher's scores combined into single scores for conduct problems and hyperactivity. These scores were categorized into below 50 th percentile (Absence of	Physician-diagnosed ICD-10 physical disorders recorded in the Military Register together with records of diagnoses in national health databases which the military register was linked to	Diagnosis of T2DM during period 1999-2004	Small number of T2DM cases (n=21) led to very imprecise measures of association. Associations were noted for severe hyperactivity (AOR: 0.5, 95% CI: 0.1-4.1), or moderate hyperactivity (AOR: 1.2, 95% CI: 0.5-3.0) with T2DM, and of	Mother's education level and somatic health problem s at age 8y	NA	Prospective design, large, population-based sample, two independent sources of child behaviors, objectively assessed / Did not use gold-	4

Table 4.2.a Cont'd

	Epidemiological Multicenter Child Psychiatric Study.			mental health problem), 50 th -90 th percentile (Moderate problems), and above 90 th percentile (Severe problems)			severe conduct problems (AOR: 1.4, 95% CI: 0.3-7.1), or moderate conduct problems (AOR: 1.4, 95% CI: 0.5-4.4) with T2DM.			standard tool for assessment of behavior problem problems, used a now-outdated questionnaire, insufficient control of confounding	
Louisiana, S (2012)33	Population-based. Subset of the	N=757-1697, ~51%M,	Assessment of aggressive behavior by CBCL 18-item	Binary variable: High CBCL aggressive	Systolic and diastolic blood pressure – average of	SBP and DPB at ages 5-, 8-,10-, and 14-y	In linear mixed effect models, high CBCL aggressive	Sex, and age stratified	NA	Prospective design, repeated assessments	5

Table 4.2.a Cont'd

	Western Australia Pregnancy Cohort (RAINE) Study	Ages 5, 8, 10, and 14 y, Age14y	subscale, by caregivers	behavior at all assessments versus Never high CBCL aggressive behavior, based on Achenbach's cut-off points (boys: ≥ 17 , girls ≥ 19)	second and third readings- were measured at clinic visits using standard, validated methods		behavior throughout childhood was associated with lower rate of increase in SBP, among boys (Beta _{Aggress} = -0.02 mmHg, 95%CI: -0.036, -0.004), Beta _{AggressXage} : -0.002 mmHg/Year, 95%CI: -0.059, -0.004), and with higher SBP among girls (Beta _{Aggress} = 0.035 mmHg, 95%CI: -0.036,	analysis presented / Confounders: Race, family income, BMI		ts of aggressive behavior using a current, validated and widely used screening questionnaire Objective assessment of outcomes. / Significant and unaddressed study
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Table 4.2.a Cont'd

							0.106), Beta AggressXage: 0.004 mmHg/Year, 95%CI: -0.013, 0.022),			attrition, insufficient control for confoundin g including no control for psychotrop ic medication use	
Keltik angas - Jarvin en, L (2006) ³⁵	A subset of the populatio n based Cardiova scular Risk in Young Finns	N=708, 44%M, Age 3- 12y, Age 24- 30y	Parents rated their children's behavior at baseline and again, 3 years later, with study specific scales derived from the	1a) Baseline- negative emotionality, 1b) Follow up- negative emotionality, 1c) Average level- negative	Left carotid intima media thickness (c- IMT) was objectively measured by ultrasound scans following standardized	Primary outcome: Carotid intima- media thickness (mm) Secondary outcome:	In linear regression analyses age- adjusted, baseline-, follow up-, and average level- hyperactivity (Adjusted beta:	Stratific ation by sex. Primary outcome analysis: Age at baseline, childhoo	Associ ation of hypera ctivity with c- IMT indep endent	Prospectiv e design, large population - based sample, long follow up,	4

Table 4.2.a Cont'd

Study (original sample=3,596) who had complete data on study variables		Health Examination Survey. The 6-item "Negative Emotionality" queried about aggression and angry outbursts. The 1-item "hyperactivity" domain inquired about motor activity and restlessness. Items were rated on 5-point Likert	emotionality 2a) Baseline-hyperactivity , 2b) Follow up-hyperactivity , 2c) Average level-hyperactivity	protocols and using the Sequoia 512 ultrasound mainframes (Acuson, CA) with 13.0-Mhz linear-array transducers. Blood pressure in 3-yr old children was assessed with ultrasound, and with a mercury or a random zero sphygmomano meter in the	SBP (mmHg)	0.13, p=0.01) were each positively associated with c-IMT among women only. Average-level hyperactivity remained associated with c-IMT in multivariate regression models (Adjusted beta: 0.11, p=0.03)	d risk factors (LDL-Chol, Systolic BP, BMI, Parental occupation status) Secondary outcome analysis: Age, and childhood systolic BP	of childh ood BMI	comprehen sive adjustment for baseline CVD risk factors / Use of study-developed measures of behavior problems not readily comparabl e with currently used scales, a
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Table 4.2.a Cont'd

			scale at baseline and on a 2-point Likert scale at follow-up. Negative emotionality scores were standardized		other children. Average was taken from 3 readings		up or average-hyperactivity-was inversely associated with SBP (Beta: -0.11, p=0.04) among men only. Negative emotionality was not associated with c-IMT (adjusted beta: -0.04, p=0.532, among men; adjusted beta: -0.01 p=0.882, among women).			single item assessed hyperactivity. Only associations with p-values <0.05 are reported
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Table 4.2.a Cont'd

177

							Among women, average-hyperactivity – but not baseline- or follow up-hyperactivity was positively associated with SBP (Beta: 0.11, p=0.02)				
Appleton, AA, (2013) ²⁸	Population-based. A subset of the offspring of participants in the Children	N=377, 58% F, Age 7y, Mean age =42.2y 41%	Children assessed by psychologists on study-specific measures of personality attributes that showed small-	Standardized scores for DP, A, and ISR	Non-fasting blood assessed for CVD-risk biomarkers. Total cholesterol (T-Chol) was assessed enzymatically.	T-Chol (mg/DL), Systolic blood pressure (SBP) (mmHg), Diabetes (Yes, No)	In sex-stratified adjusted linear regression analyses, DP was strongly associated with higher SBP, (Adjusted Beta 6.95 SE 2.24)	Age, race, study site, Small for gestational age, BMI at	Association of Distress proneness with CVD	Prospective design, population-based sample, use of psychologist ratings of	3 / 4 *

Table 4.2.a Cont'd

of Collaborative Perinatal Project study. Subset was selected with preference for racial/ethnic minorities and those with low- and high-levels of	to-medium correlation with scales of the validated Childhood Behavior Check List: Distress Proneness, (DP)= Attention problems and delinquent behavior, Attention (A)=Attention, and Inappropriate self-regulation (ISR) =Various	Blood pressure was measured in seating position with automated blood pressure monitors, and by self-reported use of antihypertensive medication. Diabetes was self-reported	among men, and with use of antihypertensive meds in women (AOR: 3.3, 95% CI= 1.6, 7.0). DP and attention were strongly associated with T-Chol, among men only, though the estimates of effect were not statistically significant (DP adjusted Beta: 5.41, SE 4.55, p=0.23; Attention	age 7, IQ at age 7, Chronic health conditions at age 7, SES	was partially independent of childhood BMI and self-reported adult-BMI	personality attributes, some outcomes were objectively measured / Relatively low response rate, study assessed personality attributes instead of behavior problems, Distress
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Table 4.2.a Cont'd

	education. Response rate: 69%		externalizing behaviors. DP scale showed low reliability				adjusted Beta: -4.9, se=3.8, p=0.20). ISR was not associated with any outcomes. In logistic regression analysis conducted only among women, DP was associated with diabetes risk (AOR: 4.1, 95% CI=1.2-13.7). Attention was also associated with diabetes			Proneness measure showed low-reliability, Diabetes was self-reported, likely some residual confounding
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Table 4.2.a Cont'd

							with moderate effect size but wide CI that included the null (AOR: 0.6, 95% CI=0.3-1.17). ISR was not associated with diabetes				
Juonala, M (2016) ⁴¹	A convenience subset sample selected from the population-based	N=311, 48% M, Mean age=14.5 y (Range: 12-18 y), Mean	Parents rated their adolescent children's behavior using study-specific scales assessing: 1) High self-	Self-regulatory behavior score, estimated as sum of high-self control and high-aggressive	Objectively measured. Coronary artery calcification was measured by computed tomography. Calcification scores were	Binary outcome: Absence of calcification (Agatston score=0), Presence of calcification	In logistic regression models, higher self-regulatory behavior was associated with lower coronary artery calcification	Age, sex, and adolescence risk factors (low-density lipoprotein	Main association was independent of adolescence	Prospective design with long follow-up, objectively assessed outcome, hierarchical and	2

Table 4.2.a Cont'd

	Cardiovascular Risk in Young Finns Study, (response rate=80%)	age 42.5 y (Range: 40 y-46 y)	control (1 item), and 2) High aggressive behavior control (6 items). Answers were binary: "Always or most of the time"=1, Otherwise=0.	behavior control scores. Score was standardized	estimated using the Agatston method.	n (Agatston ≥ 1)	(AOR: 0.59 95% CI: 0.38-0.92)	cholesterol, high-density lipoprotein cholesterol, triglycerides, systolic blood pressure, body mass index)	and adulthood body mass index, each of these tested separately	comprehensive adjustment of confounding / Selected sample (At baseline higher age, higher smoking rate, and higher triglyceride levels). Use of study-developed
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Table 4.2.a Cont'd

										measures of behavior problems not readily comparable with currently used standardized scales, a single item used to assess self-control	
Chen, Y (2017) ⁴⁴	Population based. Adolescents in 7 th to 9 th	N=162, 58% F, M=14.5 y and again at	Disruptive behavior was self-reported by participants using the Beck	1. Baseline total score for disruptive behavior,	Peripheral endothelial function was assessed using a peripheral	Delta-RHI: estimated as the difference between	In linear-regression analysis, baseline (Beta: -.346, p=0.005),	Current age, parental education,	Not tested	Prospective design, screening of disruptive	4

Table 4.2.a Cont'd

<p>grade classes from two schools in Gothenburg, Sweden, who accepted to participate in study (65 % acceptance rate)</p>	<p>M=17.5 y, M=14.5 y and again at M=17.5 y</p>	<p>Youth Inventories of Emotional and Social Impairment. Participants endorsed 20 statements with a 4-point frequency scale</p>	<p>with higher score indicating more severe behavior. 2. Mean total score for disruptive behavior= average of baseline and end of study scores</p>	<p>artery tonometry Endo-Pat device was expressed as Reactive hyperaemic index (RHI). Higher RHI indicates better endothelial function</p>	<p>end-of-study and baseline RHI values</p>	<p>and mean -over 3 years- higher disruptive behavior scores (Beta -.403, p=0.001, adjusted Beta -.332, p=0.021) were associated with worsening endothelial function, in males only.</p>	<p>school, changes in physical activity, smoking, and blood pressure</p>	<p>behaviors with a validated questionnaire. Endothelial function was objectively assessed. Exposure and outcome were assessed twice. / Small sample, relatively</p>
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Table 4.2.a Cont'd

										low response rate, algorithm used for estimation of RHI not previously validated among children, likely residual confounding	
Ramos Olazagasti, MA	Clinical sample: Caucasian white boys of	N=135 probands, 136 matched	Children with high ratings for ADHD symptoms from parents	Exposed: Boys with ADHD, free of Conduct disorder.	Participants were queried during clinical interview about their medical	Cardiovascular disease: Yes/No	No association found of ADHD with cardiovascular diseases by	Confounding was addressed by	NA	Prospective design, gold-standard assessments	3

Table 4.2.a Cont'd

(2013) ⁴²	low and middle class referred to medical center for behavior problems, and boys attending same center for other conditions. Boys with conduct	comparisons, 100% M, 6-12 y, M=41 y	and teacher were assessed in clinical diagnostic interview	Unexposed: Boys without behavior problems	history over prior 16 years of study follow up, including 5 cardiovascular diseases		bivariate Chi-square tests, $\chi^2=.00$, p -value=.97	matching on age, social class, and geographic residence		t of externalizing disorders: clinical diagnosis / Small, clinical sample, only boys included, self-reported outcome, insufficient adjustment for confounding
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Table 4.2.a Cont'd

	disorder were excluded										
Dobki n, PL (2000) ³⁶	Populatio n-based. A subset of a cohort of boys from low-SES schools in Montreal, of Canada- born, French speaking parents	N=89, 100%M , Kinderg arten age, Age 15- 16 y	Teacher ratings of the 38-item Social Behavior Questionnaire –an adaptation of Rutter’s Children Behavior’s Questionnaire- , assessed twice, in Kindergarten and again 6 years later	Participants were classified as disruptive, anxious, anxious- disruptive, or controls. To fit in any one category participants had to receive a rating on the respective scale falling above the	Objectively measured once or twice, on resting and upright seating position, using a validated automated blood pressure unit (Mennon Horizon)	SBP and DBP	2-way Anova analysis showed no group differences in mean SBP or DBP	Restricti ons at inclusio n: Age (Kinder garten), sex (boys), SES (Low) Only univaria te analysis was conduct ed.	NA	Prospectiv e design, use of two assessmen ts of disruptive behaviors, blood pressure was objectively assessed / Small sample, used a now-	2

Table 4.2.a Cont'd

				sample's 70 th twice throughout Kindergarten and elementary school				Confound ing by sex, age, and socioeco nomic status are address ed to some extent by restricti on		outdated tool for behavior assessmen t, with teachers as only source, used single reading of blood pressure in some participant s, insufficient control of confoundin g, no baseline
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Table 4.2.a Cont'd

										measure of outcome		
Cross sectional studies												
Hailpern, S (2014) ³⁸	Population-based: Adolescents in NHANES for years 1999-2004	N=4,524, 52% M, Mean age =15.0 y SD=2.8y	A doctor or health professional asked participants about receiving a diagnosis of ADHD. Children with ADHD also self-reported on using CNS stimulant medication.	Categorical variable: 1) No ADHD, 2) ADHD without CNS stimulants, 3) ADHD with CNS stimulants	Trained health workers measured Blood pressure using a mercury sphygmomanometer, and following a standardized protocol. The average measure of 3 readings was calculated for SBP and DBP and values were	Continuous BP variables: SBP and DBP corresponding percentile s	Categorical: 1) Hypertensive: Either	In linear regression analyses neither ADHD w/o stimulants nor ADHD w/stimulants was associated with SBP or DBP percentiles, in girls or boys	Analyses were sex-stratified. Models adjusted for age, BMI, race, blood glucose, eGFR, CRP, Househ	NA	Large, population-based sample / Cross-sectional design, self-reported ADHD	3

Table 4.2.a Cont'd

			Participants 16 y old or younger had a proxy respond for them		transformed into age-, sex-, and height -adjusted percentiles	SBP or DBP >= 95 th percentile 2) Pre- hypertensi ve: 90 th percentile < SBP or DBP <=95 th percentile 3) Normoten sive: SBP and DBP <90 th percentile		old income level, total Chol, Pulse			
Louis e, S	Populatio n-based.	N=757- 1697,	Multi- informant	CBCL aggressive	Systolic and diastolic blood	Continuou s	In linear regression	Sex stratifie	Associ ation	Population based, use	4

Table 4.2.a Cont'd

(2012) 33	Subset of the Western Australian Pregnancy Cohort (RAINE) Study	~51 %M, Age 14y	assessment of aggressive behavior at age 14Y: 18-item CBCL by parents, 17-item YSR, by teens, 20-item TRF, by teachers	behavior scores at 14y, range: 0-36 YSR aggressive behavior score at 14y, range: 0-34 TRF aggressive behavior 14y, range: 0-40	pressure – average of second and third readings- were obtained by validated protocols Fasting blood samples were assessed for CVD biomarkers. Total-Chol and Triglycerides were assessed enzymatically, glucose assessed by automated Technicon Axon analyzer, Insulin	variables: SBP, DBP, Total-Chol, LDL-Chol, and Triglycerides at age 14y	models, CBCL aggressive behavior score was associated with HOMA-IR, among girls only (Beta=0.010, 95% CI: 0.002-0.017). TRF aggressive behavior score was inversely associated with DBP, among boys only, and the association remained after adjustment for confounders,	d analysis presented / Confounders: Race, family income, smoking	of CBCL aggressive behavior or with HOMA in girls was only partiall y indepe ndent of BMI	of gold-standard tools for screening of externalizing behaviors with multiple reporters, examined wide range of CVD and diabetes risk markers /
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Table 4.2.a Cont'd

					<p>assessed by RIA (Tosoh). HOMA-IR calculated as: Insulin (uU/mL) x glucose (mmol/L)/22.5, LDL-Chol calculated by Friedewald formula</p>		<p>BMI, and smoking (adjusted beta: -0.165, 95%CI: -.301, -0.0028).</p> <p>TRF score was associated with triglycerides among boys (Adjusted Beta: 0.011, 95% CI: 0.002-0.020), and among girls (Adjusted Beta: 0.013, 95% CI: 0.001-0.025).</p> <p>TRF was associated with total-Chol</p>			<p>Cross sectional-design,</p>
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Table 4.2.a Cont'd

							(Adjusted Beta: 0.018, 95% CI: 0.003-0.032), and with LDL-Chol (Adjusted Beta: 0.015, 95% CI: 0.002-0.027) among boys only. No associations found of aggressive behavior with blood pressure in girls				
Osika, W (2011) ⁴⁵	Children from two schools in the	N=248, 45%M, Mean age	Disruptive behaviors were self-rated by	Disruptive behavior score	Endothelial function assessed by reactive	Log-transformed RH-	In multivariate linear regression analysis, higher disruptive	Analyse s were sex-stratified	Unclear	Objective measure of outcome, use of a	3

Table 4.2.a Cont'd

	Göteborg region of Sweden that volunteered (46% participation rate) to participate in study	14.0 y SD=1.0 y	participants with the 20-item Beck Youth Inventories-disruptive behavior subscale. Total scores (the sum of items) were transformed by Stata's Inskew0 procedure to minimize skewness		hyperaemia arterial tonometry (RH-PAT) with the EndoPAT device (Itamar Medical). The procedure was shown to be reliable in this sample of children. A higher RH-PAT score indicates better endothelial function	PAT scores	behavior was associated with better endothelial function (Adjusted beta: 0.09, 95% CI=0.027-0.154) among boys, but not among girls (Adjusted beta: -0.04, 95% CI= -0.10-0.02)	d, and regression models were adjusted for age, maternal and paternal education, smoking status, number of siblings, birth order, and pet		validated, currently most used tools for screening of adolescent externalizing behaviors / Cross-sectional design, self selected sample, possibly with more deviant boys
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Table 4.2.a Cont'd

								ownersh ip, number of family member s per room		opting out. Unclear whether regression models are adjusted for BMI	
Shar ma, S (2011) ³⁴	Subset of participa nts (Those with complete data= 85%) of a communi ty-based lifestyle modificat ion	N=127, 47%M, Ages 10.7y (range 9- 12y)	The Behavioral Assessment for Children (BASC-2), Parent and Child versions were used to assess externalizing problems among	Externalizing Problems, T- score Inattention/ Hyperactivit y, T-score	HOMA-IR was calculated from glucose and insulin concentrations determined in 12-h fasting blood samples obtained from participants at clinic visit.	Log- transform ed HOMA- IR values	In hierarchical multiple linear regression analysis, Externalizing Problems t-score (Adjusted beta: 0.225, p-value <0.05) and Inattention/Hyp eractivity t-score (Adjusted beta: 0.251, p-value	Gender, age, pubertal state, family SES, interven tion group	Adjust ment for waist circum ferenc e, in fact, strengt hened the associa tions	Assessmen t of externalizi ng problems using a valid, currently used tool and multiple raters, Objective	3

Table 4.2.a Cont'd

<p>program to reduce the risk for T2DM study in inner-city African American children with BMI ≥ 85th percentile free of metabolic disease or taking medication</p>			<p>participants: The “Externalizing problems” composite, from parent’s reports, and the “Inattention/hyperactivity” composite, from children’s reports, were used in these analyses. BASC-2 has been normed on general population</p>				<p><0.01) were positively associated with HOMA-IR</p>		<p>reported</p>	<p>assessment of study outcome / Cross-sectional design, small sample, restricted to overweight and obese children participating in an intervention, results possibly biased due</p>
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Table 4.2.a Cont'd

	ons affecting body weight		samples. Raw scores from this study were T- transformed							to interventio n spill-over effects	
Pine, DS (1996) ³⁹	Subset of younger brothers of all adjudicat ed juvenile delinque nt males in NYC. Nearly a third was obese, and a	N=102, 100%M, Age: 8.4 y SD=1.5	CBCL, and DISC 2.3 – parent versions- were administered to by trained non-clinician interviewers during home visits. From the CBCL, the broad band Externalizing	CBCL- Externalizing score, (EXT) CBCL- Aggression score, (AGG) CBCL- Delinquency score, (DEL) DISC- Disruptive Behavior	Blood pressure was assessed at clinic visit by pediatrician using a mercury sphygmomanom eter and with the participant seating and after resting for 30 minutes. Two readings were taken and averaged. SBP	Continuou s variables: SBP, DBP, Mean BP Binary variable: High BP= either of High SBP or High DBP	In multivariate regression analysis, EXT was positively associated with SBP (Adjusted beta: 2.3, p<=0.01), DBP (Adjusted beta: 2.0, p<=0.05), and Mean BP (Adjusted beta: 2.8, p<=0.01).	Restricti on: All- boys study, boys taking medicati ons were exclude d, N=18. Confoun ders were:	Associ ation indepe ndent of obesity	Gold standard assessmen t of externalizi ng problems including diagnostic interview, objective assessmen t of outcome	3

Table 4.2.a Cont'd

	<p>quarter had high blood pressure</p>		<p>scale, and its two internal Aggression and Delinquency subscales were used. Scores were z-transformed. From DISC, three diagnostic measures were used: ADHD, Oppositional Defiant Disorder (ODD) and</p>	<p>(DISC-D), binary: Yes= At least one of ADHD, ODD, or CD diagnosed No= None of ADHD, ODD, or CD diagnosed</p>	<p>was determined at Korotkoff phase I, and DBP was determined at phase V. Mean BP was = 1/3 SBP + 2/3 DBP. SBP or DBP were considered high if $\geq 90^{\text{th}}$ percentile for age and gender published by Second Task Force on BP Control in Children</p>		<p>In logistic regression analysis DEL (AOR: 2.09, 95% CI=1.16-3.76), and DISC-D (AOR: 4.89, 95% CI=1.11-21.6) were associated with High BP. Smaller and marginally non-significant associations were noted too for AGG and EXT.</p>	<p>Age, height, Tanner stage, social class, obesity, ethnicity</p>	<p>/ Cross-sectional design, small and self-selected sample, single, DBP was determined using the Korotkoff V instead of Korotkoff IV used for national BP recommendations</p>
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Table 4.2.a Cont'd

			Conduct Disorder (CD).								
Pajer, K (2016) ⁴⁶	Clinical sample drawn from the Girls Coping with Stress Study, Ohio State University Medical School	N=60, 100%F, Mean age: 15.7y SD=0.32	Psychiatric diagnoses of conduct disorder (CD) and anxiety (AD) or depressive disorder (DD) were made at a clinic visit based on structured interviews using the computerized Diagnostic	CD (Yes, No) AD (Yes, No) DD (Yes, No)	Endothelial function was assessed by reactive hyperaemia arterial tonometry (RH-PAT) conducted with a Hokanson EC6 plethysmograph (DE Hokanson Inc). Data were scored twice by a same person blind to participant's	PCFVR, average score	Results from unclearly described analyses using linear regression appear to show no association of CD with endothelial function. However, a regression term for interaction of CD with AD was statistically significant, suggesting that	BMI, and Race	NA	Gold-standard method for assessment of CD, objective measure of endothelial function / Cross-sectional design, very small sample, Incomplete and	3

Table 4.2.a Cont'd

			Interview Schedule for Children, DISC, conducted separately with parents and youth		other info. Scores were averaged, higher score indicating healthier endothelial function		girls with conduct disorder free of AD might have healthier endothelial function			confusing description of statistical analyses and presentatio n of results difficult interpretat ion
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*Evidence pertaining to SBP and blood lipids, each objectively assessed by study was graded G=4. Evidence pertaining to self-reported diabetes was graded G=3.

Table 4.2. b: Cross-sectional studies that examine whether CVD risk factors or T2DM are risk factors for ADHD

Author (Year of publicati on)	Setting: Populatio n-based/ Clinical sample/ Convenie nce sample	Sample size, Gender, Age at exposure assessme nt, Age at outcome assessme nt	Exposure assessment: Clinical interview/ Parent-Teacher questionnaire/ Self-reported	Exposure measure	Outcome assessment: Objectively measured/ Self- reported	Outcome measure	Results	Stratificati on/ Matching/ Confoundi ng adjustment	Assoc. independen t of BMI	Advantage s/ Limitation s	G
Chen, HJ (2013) ³²	Populatio n based: The LHID2005 database, containin g complete	N=25,81 2, 80%M, Age=8.6 y SD=2.7y	T2DM was considered present if participants had records of at least two consensus T2DM diagnoses	T2DM (Yes, No)	ADHD was considered present if participants had records of: Clinician- made diagnosis of ADHD based on the use of diagnostic	ADHD by clinical diagnosi s (Yes, No)	In multivari ate logistic regressio n T2DM was positively	Exposed and unexposed were matched on age, sex, and index year.	Associatio n independ ent of obesity	Large size, population based study. Clinical diagnosis of ADHD and T2DM /	3

Table 4.2.b Cont'd

	<p>claim data and registration information files for 1,000,000 randomly selected individuals in the Taiwan National Health Insurance Program</p>		<p>in the insurance's database</p>		<p>tests and physical examination</p>		<p>associated with ADHD (AOR: 2.75, 95% CI= 1.82, 4.16)</p>	<p>Adjustment was made for matching factors plus geographic region, and obesity (yes, no)</p>	<p>Cross-sectional design, passive ascertainment of exposure and outcome may have led to measurement error in assessment of ADHD and T2DM, error that could be systematic – adolescents with T2DM/obesity</p>
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Table 4.2.b Cont'd

										ty more likely to be tested for behavior problems-leading to overestimation of effect, and incomplete control for confounding	
Meyer, T (2017) ⁴⁰	Population-based: a subset of the German Health Interview and examination	N=6,922 49.9%M, Mean Age= 14.6 y SD =2.0 (range 11-17 y)	Medical personnel measured blood pressure at the clinic visit using a sphygmomanometer and the oscillometric	Hypertension (Yes, No) was defined as SBP or DBP above the age-, sex-, and height-	Parents reported whether their child had ever received a doctor-made diagnosis of ADHD. Parents also completed the 5-item SDQ-	1) ADHD diagnosis, self-reported (Yes, No) 2) Suspected ADHD	In multivariate logistic regression analysis, both SBP and DBP	Analyses were adjusted for: sex, age, BMI, psychotropic medication	Association independent of BMI	Large, population based sample, objective assessment of outcome /	3

Table 4.2.b Cont'd

	<p>on Survey for Children and adolescen ts, May 2003- 2006</p>		<p>technique. Two independent readings taken on resting position were collected and averaged.</p>	<p>adjusted 95th percentile value for the pediatric population published by the American National High Blood Pressure Education Program</p>	<p>hyperactivity/inatte ntion subscale.</p>	<p>(=1, if SDQ-HI score >=7, =0, otherwis e) 3) Categori cal variable: -ADHD diagnosi s + Suspecte d ADHD -Only one of ADHD diagnosi s or</p>	<p>were inversely associate d with self- reported ADHD (SBP AOR: 0.97, 95%CI= 0.96- 0.99), (DBP AOR: 0.97, 95%CI= 0.95- 0.99)</p>	<p>use, and 25(OH)D</p>		<p>Cross- sectional design, use of self- reported ADHD diagnosis and use of SDQ ratings from parents only, insufficient control of confounding</p>
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Table 4.2.b Cont'd

						Suspecte d ADHD -Neither ADHD diagnosi s nor Suspecte d ADHD					
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Appendix for Chapter 4

Table A.4.1. a: Summary of associations reported by all studies, by study outcome

Outcome	Associations with		Risk of outcome was		Risk of outcome		Risk of outcome	
	the outcome tested		elevated among the		was the same		was reduced among	
	N	Average	% (n/N)	Average	%	Average	%	Average
		G		G	(n/N)	G	(n/N)	G
T2DM / HOMA-IR	12	3.4	75 (9/12)*	3.6	25 (3/12)	2.9	--	--
Blood pressure	14	3.6	36 (5/14)	3.8	43 (6/14)	3.3	21 (3/14)	4.0
Subclinical atherosclerosis	3	3.3	67 (2/3)	3.0	33 (1/3)	4.0	--	--
Endothelial function	3	3.3	33 (1/3)	4.0	--	--	67 (2/3)	3.0
Blood lipids	6	4.2	100 (6/6)**	4.2	--	--	--	--

G= Evidence quality grade (range 0-5)

* Includes 3 non-statistically significant associations

** Includes 2 non-statistically significant associations

Table A.4.1b: Summary of associations reported by studies, by timing of outcome assessment (childhood/adolescence or adulthood) and by study outcome

Outcome	Associations with the outcome tested		Risk of outcome was elevated among the exposed		Risk of outcome was the same among exposed and unexposed		Risk of outcome was reduced among the exposed	
	N	Average G	% (n/N)	Average G	% (n/N)	Average G	% (n/N)	Average G
Studies that assessed outcomes in childhood or adolescence								
T2DM / HOMA-IR	5	3.6	100 (5/5)	3.6	--	--	--	--
Blood pressure	7	3.6	29 (2/7)	4.0	29 (2/7)	2.5	43 (3/7)	4.0
Subclinical atherosclerosis	0	--	--	--	--	--	--	--
Endothelial function	3	3.3	33 (1/3)	4.0	--	--	67 (2/3)	3.0
Blood lipids	4	4.3	100 (4/4)	4.3	--	--	--	--
Studies that assessed outcomes in adulthood								
T2DM / HOMA-IR	7	3.6	57 (4/7)*	3.5	43 (3/7)	2.9	--	--
Blood pressure	7	3.7	43 (3/7)	4.0	57 (4/7)	3.5	--	--
Subclinical atherosclerosis	3	3.3	67 (2/3)	3.0	33 (1/3)	4.0	--	--
Endothelial function	0	--	--	--	--	--	--	--

Table A.4.1b Cont'd

Blood lipids	2	4	100	4.0	--	--	--	--
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(2/2)**

Table A.4.1b Cont'd

G= Evidence quality grade (range 0-5)

* Includes 3 non-statistically significant associations

** Includes 2 non-statistically significant association

Figure A.4. 1: Pubmed/Medline Search terms

**Search (((((((((((attention deficit and disruptive behavior disorder)) OR child attention problems) OR child inattention) OR hyperactivity problems) OR (attention deficit and hyperactivity problems)) OR conduct disorder) OR child conduct problems) OR externalizing behavior problems) OR externalizing disorders) OR child behavior problems)) AND (((((((((((cardiovascular diseases) OR hypertension) OR blood pressure) OR insulin resistance) OR hyperglycemia) OR hyperinsulinemia) OR diabetes mellitus, type 2) OR atherosclerosis) OR cholesterol) OR triglycerides) Sort by: Best
Match Filters: Full text; Publication date from 1980/01/01 to 2018/12/31; Humans; English**

Chapter 5:

Conclusions

Research conducted over the last decade has unveiled a positive association of internalizing problems, including anxiety and mood disorders, with the development and worsening of cardiometabolic disorders among adults¹⁻³. Current knowledge suggests that the relationship is one likely to be established in early life, and also that common externalizing problems such as hyperactivity, conduct, and attention problems may too contribute to increase the risk for cardiovascular diseases and T2DM. These disorders and its biological precursors, once considered diseases of the old, are now increasingly diagnosed among the young⁴⁻⁶. Currently, only a fraction of CVD/T2DM can be explained by known risk factors and the identification of new ones, especially early-life risk factors, is an explicit top priority in public health research^{4,7,8}. Very little studies have examined these questions. This dissertation sought to shed light into these important matters.

Summary of findings:

Chapter 2 of this dissertation describes research conducted to examine the prospective relationships between childhood internalizing and externalizing problems with clinically significant high levels of 3 biological markers known to be causally associated with CVD and T2DM development: HOMA-Insulin Resistance index, LDL-Cholesterol, and Triglycerides. These relationships were investigated using data from a large, population based cohort study (ALSPAC) assembled in the UK in the years 1990/2^{9,10}. Findings showed that children with externalizing problems (hyperactivity problems or conduct problems) have higher risk of developing high levels of HOMA-IR (insulin resistance) and blood triglycerides at age 17. These children were also more likely to be obese by age 15. On the other hand, this research found that

compared to other children, children with internalizing problems (emotional problems) had decreased risk of developing high levels of triglycerides by age 17 and were also less likely to be obese at age 15. These associations persisted after comprehensive adjustment for confounding by demographic, socioeconomic, maternal and environmental factors, family history of CVD and T2DM, pregnancy and birth outcomes, breastfeeding and after controlling for study attrition bias. Associations also persisted when hyperactivity, conduct, problems, and emotional problems were adjusted for each other. The associations of childhood hyperactivity and conduct problems with higher HOMA-IR and with clinically significant high triglyceride values that this research found are novel as no prior studies investigated these questions prospectively in a cohort of healthy children. But these results are consistent with findings from two prior studies that showed an association of ADHD at age 13 with incident T2DM and prevalent dyslipidemia at age 18¹¹ and with cross-sectional associations of aggressive behavior at age 14 with triglycerides (among boys and girls) and with HOMA-IR (among girls only)¹². Control for confounding was minimal in both these studies, limited to basic demographics. This dissertation's research adds to knowledge from prior studies in three ways: first, it shows that increased CVD and T2DM risk in adolescence is already predicted by childhood (as opposed to adolescence) levels of hyperactivity and conduct problems; second, it shows the first evidence to date of a prospective positive association of externalizing problems with clinically significant levels of triglycerides in adolescence; third, it reports effect estimates that are adjusted for a comprehensive set of confounding factors and that are, therefore, less biased than effects estimates reported by prior studies; and fourth, it shows for the first time in the same report that externalizing and internalizing problems are differentially associated with CVD/T2DM in children and adolescents. This dissertation's findings of inverse associations of internalizing problems with obesity are consistent with some prior findings of

similar relationships of depressive symptoms with obesity in children^{13,14} but it extends that knowledge by providing the first evidence of a prospective inverse association with clinically significant values of triglyceride that persisted to robust adjustment for confounding.

Chapter 3 describes research conducted to elucidate the mechanism/s underlying the positive associations identified in Chapter 2 of childhood hyperactivity and conduct problems with clinically significant high levels of triglycerides at age 17. Causal mediation methods^{15,16} that account for the partial overlapping of mediation pathways by several mediators were used to determine the extent to which the effects of hyperactivity and conduct disorder were explained, or mediated, by a series of potential mediators. Specific potential mediators were selected based on the current literature as factors that have been linked to both, externalizing symptomatology and increased levels of triglycerides and included: hours of sleep¹⁷, aspects of diet^{18,19}, physical activity²⁰, consumption of alcohol²¹, smoking²¹, body mass index and changes of body mass index²². Analyses found relatively low prevalence in the sample of some of the mediators tested, compared with US cohorts²³, and more recent UK cohorts²⁴. Hyperactivity and conduct problems were strongly associated with some (BMI, sleep hours, SSB) but not all (alcohol, smoking) of the mediators tested. Triglyceride levels were weakly associated with a few of the mediators (smoking, alcohol, dietary fat composition) and was only strongly associated with BMI. Causal mediation analyses found that the associations of childhood hyperactivity and conduct problems with clinically triglycerides at age 17 are mostly explained by direct effects, that is, effects are largely not mediated by the factors considered. Specifically, it was estimated that, at most, 20 % of the total effects of hyperactivity and conduct problems on triglycerides were explained by pathways involving these specific mediators, and the mediated effects were largely accounted for by body mass index. These findings are supported by a strong study design and methodology and

they are relevant given that no other studies have conducted formal assessment of mediation of these relationships. Our results are consistent with findings of relationships persisting after regression adjustment for BMI in a few studies that found associations of aggressive behavior with HOMA-IR¹², and of ADHD with T2DM and dyslipidemia ¹¹.

Chapter 4 describes research conducted to summarize and assess consistency of the current literature that investigates the relationship of childhood externalizing problems with increased CVD/T2DM risk over the life course. The developmental timing (i.e. childhood, adolescence, young adulthood, mid-adulthood, older adulthood) at which elevation of risk becomes evident and whether the relationships are mediated by increased body adiposity were additional questions of interest. A systematic review of the literature was conducted following PRISMA guidelines. A search of 2 electronic databases (Pubmed/Medline and Web of Science) led to the identification, and selection (based on pre-defined inclusion and exclusion criteria) of 20 original research reports. Studies were graded for quality of evidence. This systematic review found solid evidence, based both on consistency of reports and quality of evidence, of a positive association of externalizing problems with increased risk of T2DM and with elevated levels of HOMA-IR in childhood and adolescence. This evidence came mostly from cross-sectional studies. Evidence was equally solid, and again, mostly cross-sectional, in support of an association with higher levels of blood lipids (T-Cholesterol, LDL-Cholesterol, and triglycerides) in adolescence. Evidence that these effects may persist into adulthood was less clear, possibly owing to the fact that prospective studies that tracked individuals into adulthood were of lower quality, with a tendency to rely on less valid externalizing assessment methods and on self-reports of T2DM and CVD related outcomes. This review found also some evidence of positive associations with outcomes other than T2DM or blood lipids, including prospective worsening endothelial function

(in adolescence) and prospective subclinical atherosclerosis (mid-adulthood) but research on those outcomes was too sparse for an assessment of consistency. Although no study applied formal assessments of mediation, evidence from regression analyses suggests that positive associations were independent of body adiposity.

In summary, together, the results from the empirical research (Chapters 2 and 3) and the literature review (Chapter 4) support a longitudinal association of childhood hyperactivity and conduct problems with increased risk of T2DM, elevated HOMA-IR and clinically significant high levels of blood lipids in adolescence. Our findings suggest that these effects are to a large extent independent of body adiposity and unfavorable health behaviors.

Implications of findings

The findings in this research have implications at various levels. First, externalizing problems are identified as a novel childhood risk factor for early development of CVD/T2DM risk, directly addressing a current priority of public health research while also providing newer support to hypotheses of the childhood origins of chronic diseases. Second, these results add to the evidence that physical health is impaired in children with externalizing problems and suggest that CVD/T2DM risk –specifically, HOMA-IR and blood lipids- might need to be monitored in adolescents with a history of externalizing problems. Third, findings that CVD/T2DM risk is elevated in adolescents with a history of childhood behavior problems regardless of body adiposity and poor health behaviors suggests that current guidelines for monitoring of cardiometabolic risk may not be adequate and that risk should be monitored in all children with externalizing problems, not just obese or at-risk of obesity adolescents. Furthermore, if confirmed by future studies, this

research also suggests that lifestyle modification approaches might not be enough to reduce CVD and T2DM risk among these children. Fourth, this research may also contribute to expand understanding of the processes of biological embedding of mental health problems. That childhood externalizing, but not internalizing behavior problems, are associated with CVD and T2DM mainly through pathways that do not involve adiposity or health behaviors may suggest of relevant neurobiological differences between these two overarching domains of psychopathology. Proposed alternative pathways include pro-inflammatory and pro-insulinemic effects triggered by stress-related disruption of the SNS-HPA axis in psychopathology. Research on how internalizing and externalizing psychopathology, both associated with greater stress, differ with regards to those processes could be aided but our findings.

Future research

Future research studies should seek to replicate these findings and to further expand this newly gained knowledge. This research supports a number of recommendations for next studies.

First, studies should ideally be conducted in more recent cohorts known to bear higher prevalence of obesity and unhealthy health behaviors.

Second, studies should strictly rely on the use of well-validated measures of externalizing symptomatology or diagnoses, objective assessments of CVD/T2DM risk, and employ prospective designs, ideally - in particular for studies with short follow up - relying on both baseline and end-of-study assessments of study outcomes. In fact, research is critically needed to obtain normative data on cardiometabolic risk parameters in children. The use of multiple informants of externalizing behavior has been shown to increase validity of assessments, and external informants

–as opposed to self- are known to be particularly more valid for assessment of externalizing psychopathology²⁵.

Third, studies should also examine whether CVD and T2DM risk varies among adolescents with childhood-limited, adolescence-onset, and childhood-onset persistent externalizing problems, and whether different phenotypic sub-types including, inattentive, hyperactive, and more antisocial types, may have critical bearings on risk for certain outcomes or might have unique developmental sensitive points. Research from the very few studies that have done so (among adults) supports the existence of these differences and further suggest that differences might vary by sex/gender^{26,27}. Future studies should include measures that allow the characterization of these subtypes using stratified sampling approaches to ensure adequate power to study these relationships.

Fourth, more research is needed into the mechanisms that underlie the relationships elucidated by this research. Perhaps more refined hypothesis are needed with regards to health behaviors. For example, sleep anomalies other than short sleep hours may be involved. Approaches for dietary assessments that overcome participants misreporting problems are needed. Furthermore, future studies that follow children across developmental stages should assess health behavior mediators on more than one occasion as habits are likely to change throughout follow-up, in part just due to normative effects.

Fifth, these findings support expanded research into the role of SNS-HPA axis disruption in mediating the relationships reported here. Sixth, studies should seek to measure and control for confounding other than basic demographics. Our research in Chapters 2 and 3 could be used as a guide for that manner. Family history of psychiatric diseases – including maternal depression -, diabetes, and cardiovascular disorders are all associated with externalizing psychopathology and

with CVD risk therefore failing to adjust for these factors may likely bias effect sizes against the null. Pregnancy and birth outcome are additional likely confounders that this dissertation research accounted for, but not by any prior studies. Common genetic and/or neurobiological vulnerabilities could, in addition, be an alternative explanation (confounding) for the relationships examined in this review. Future research should investigate these relationships as well.

Lastly, internalizing and externalizing comorbidity is another key aspect that studies should consider, given that comorbidity is highly prevalent, given that, externalizing and internalizing problems seem to exert opposite effects on obesity and triglycerides (at least until adolescence) as we report, and given the known differing relationships of internalizing and externalizing problems with possible mediators such as smoking and alcohol use.

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