Physical- and sedentary activities, muscle strength and prevention of type 2 diabetes, cardiovascular disease, and raised levels of their biological risk factors in youth and adults

An investigation based on observational studies

Papers

Paper I

Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A meta-analysis. JAMA: The Journal of the American Medical Association. 2011;305(23):2448-55.

Paper II

Grøntved A, Ried-Larsen M, Møller NC, Kristensen PL, Wedderkopp N, Froberg K, Hu FB, Ekelund U, Andersen LB. Youth screen time behaviour is associated with cardiovascular risk in young adulthood (The European Youth Heart Study). European Journal of Preventive Cardiology. 2012;(Epub ahead of print).

Paper III

Grøntved A, Rimm EB, Willett WC, Andersen LB, Hu FB. A Prospective Study of Weight Training and Risk of Type 2 Diabetes in Men. Archives of Internal Medicine. 2012;172(17):1306-12

Paper IV

Grøntved A, Ried-Larsen M, Møller NC, Kristensen PL, Froberg K, Brage S, Andersen LB. Muscle strength in youth and cardiovascular risk in young adulthood (The European Youth Heart Study). *British Journal of Sports Medicine.* 2013. (Epub ahead of print).

Paper V

Grøntved A, Ried-Larsen M, Ekelund U, Froberg K, Brage S, Andersen LB. Independent and combined association of muscle strength and cardiorespiratory fitness in youth with insulin resistance and beta-cell function in young adulthood (The European Youth Heart Study). *Diabetes Care.* 2013. (Epub ahead of print).

Paper VI

Grøntved A, Ried-Larsen M, Froberg K, Wedderkopp N, Brage S, Kristensen PL, Andersen LB, Møller NC. Screen time viewing behaviors and isometric trunk muscle strength in youth. *Medicine & Science in Sports & Exercise.* (accepted for publication)

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Anders Grøntved
Odense, December 2012

List of abbreviations

BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CRF	Cardiorespiratory fitness
CVDs	Cardiovascular diseases
EYHS	European Youth Heart Study
FFQ	Food frequency questionnaire
HDL-C	High density lipoprotein cholesterol
HOMA-B	Homeostasis model assessment of β-cell function
HOMA-IR	Homeostasis model assessment of insulin resistance
HPFS	Health Professionals Follow-up Study
HR	Heart rate
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
ISCED	International Standard Classification of Education
METs	Metabolic Equivalent Task
MVPA	Moderate and vigorous physical activity
N	Newton
OR	Odds ratio
RR	Relative risk
SD	Standard deviation
T2D	Type 2 diabetes
TV	Television
WC	Waist circumference

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Introduction

Type 2 diabetes, cardiovascular diseases, and their biological risk factors

Worldwide, type 2 diabetes (T2D) and cardiovascular diseases (CVDs) are major chronic diseases that cause premature death, morbidity, and disability. CVDs are the leading causes of death, representing about 30% of all deaths in the world (1). Individuals with T2D are at major risk of complications and diseases that include nerve damage (neuropathy), kidney damage (nephopathy), eye damage (retinopathy), CVDs, and 50% or more deaths among these patients are caused by CVDs (2). The individual, societal, and economical burden of T2D and CVDs in Denmark and the rest of the world are therefore enormous.

While the levels of some biological risk factors for these diseases have decreased or changed little in the past decades in western populations in particular (for example systolic blood pressure (BP) (3) and total cholesterol (4)), other risk factors such as fasting glucose and body mass index (BMI) have increased in lower-income populations, in the developing world, and in some western countries. The estimated global age adjusted mean fasting glucose- and BMI values have increased by 0.07 mmol/l and 0.4-0.5 kg/m^2 per decade respectively since 1980 (5, 6). The most recent world wide estimates of T2D prevalence based on systematic evaluation of health examination surveys and epidemiological studies estimate that 285-347 million individuals have T2D (5, 7), and this number is projected to increase to 439 million by year 2030. Data from the Danish National Diabetes Register suggest that the prevalence of T2D have increased from 1995-2007 with 6% per year and in 2007 4.2% of the total Danish population had T2D (8). Although the increase can be attributable to factors such as demographic changes (e.g. aging population), improved detection of undiagnosed diabetes, better treatment for T2D, an increase in the populations exposure to risk factors for T2D are very likely also an explanation (e.g. obesity and sedentary lifestyle). While T2D is still a rare condition in youth, increasing incidence rates have been observed in the U.S. possibly due to the increase in youth obesity (9). Similar trends in the prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), considered as precursors of T2D, have also been reported in youth (10). Despite substantial reductions in the incidences of CVDs and CVD mortality in Denmark and in other Western countries, the incidence of CVDs is still high (1). According to the latest statistics from the Danish Heart Association more than 15.000 yearly deaths and 54.000 yearly hospitalizations are

due to CVDs in Denmark (11). To further curb the substantial burden due to T2D and CVDs in Denmark and globally, primordial- and primary prevention is of great importance. Identification of which factors are important for the development of T2D and CVDs is essential to prevention. One recognized exposure with significant importance for both prevention of T2D and CVDs is physical activity.

Physical activity and risk of type 2 diabetes and cardiovascular diseases

The benefits of being regular physically active or having a high cardiorespiratory fitness for prevention of CVDs and T2D have been addressed and recognized in numerous scientific studies in the past three decades in particular. Comprehensive quantitative assessments of the benefits of aerobic moderate and vigorous physical activity (MVPA) or cardiorespiratory fitness based on all available and published studies have been done in several independent reports (12-18). In a recent meta-analysis based on 33 independent studies, aerobic type- or non-specific (in terms of type) physical activity during leisure, occupation, and during transportation, were associated with 25% risk reduction of coronary heart disease (CHD) when comparing highest and lowest categories of physical activity (12). Another meta-analysis based on 24 independent studies reported risk reduction of 15% for CVDs per 1 MET (3.5 ml O_2/min/kg) difference in cardiorespiratory fitness (14). For T2D, a meta-analysis conducted in 2007 found that regular engagement in physical activity of at least moderate intensity (aerobic type- or non-specific physical activity) was associated with 30% reduction in the risk of T2D comparing highest and lowest categories of activity level (13). Recent global conservative evaluations of population attributable fractions estimate that not engaging in the recommended MVPA level of at least 150 min/week causes 5.8%, 7.2%, and 9.4% of all cases of CVDs, T2D, and total deaths respectively (19).

The cumulative evidence from observational studies on the benefits of aerobic physical activity is supported by randomized controlled trials conducted in various populations including among children and youth. The effect of engaging in aerobic physical activity on blood lipid levels, adiposity, blood pressure, and glycemic control has been evaluated among individuals with prevalent CVDs and T2D, children, youth and adults with prevalent risk factors (e.g. obesity), and among healthy individuals (20-23). Based on the pool of evidence from observational and experimental studies a number of organizations and authorities have issued physical activity guidelines in the past decades. Nonetheless, it was not until 2008 that the federal government in the US

released its first official national Physical Activity Guidelines for Americans (24), which main recommendation include that adults should accumulate at least 150 min of aerobic MVPA per week and children and youth should accumulate 60 min/day to promote and attain health benefits.

The current recommendations for physical activity also emphasize that the MVPA endorsed is in addition to what is referred to the baseline activity – the usual light or sedentary activities of daily living (24-26). Due to rapid changes in leisure, workplace, and personal transportation habits in our society it is very likely that the baseline activity is reduced to a minimum in many populations. Assuming that engagement in activity in the lower spectrum of the physical activity continuum (i.e. lighter intensity activity (1.6-2.9 METs)) has health benefits, the public health impact of this reduction may be substantial and attributable to increases in particular activities such as television (TV) viewing. Despite the overwhelming evidence to support regular engagement in physical activity for lifelong health, the majority of previous studies have reported on the health benefits of aerobic type physical activity such as walking, jogging, and on the benefits of non-specified moderate or vigorous physical activity. Remarkably few studies have addressed the associations of types of activity (beyond aerobic activity) including muscle strengthening activities and types of activities that are considered being sedentary (≤1.5 METs) or of light intensity with health outcomes. Furthermore, while a substantial number of large scale observational studies have shown that a low level of cardiorespiratory fitness in adults is a major risk factor for various health outcomes, more limited evidence exist from well conducted studies for other components of health related physical fitness such as muscle strength.

Total sedentary behavior, television viewing, and other screen based behaviors

In the past decades a remarkable growth in the availability and use of electronic media has occurred. These include use and availability of TV, computers, and video games (e.g. Playstation). More recently, the wide availability and use of tablets and smartphones have also increased profoundly (27). Apart from working and sleeping, TV viewing is the most commonly reported daily activity in many populations around the world (28-30). Among adults the average TV viewing time is about 3-4 hours/day in western countries (28, 29) and reports from the U.S. have indicated up to 5 hours/day of viewing time (30). In Denmark the most recent statistics suggest that both children and adolescents on average spend more than 2 hours/day viewing TV and adults spend almost 3.5 hours/day

(31). During the last decade TV viewing time has markedly increased in Danish children, youth, and adults as illustrated in Figure 1 (32).

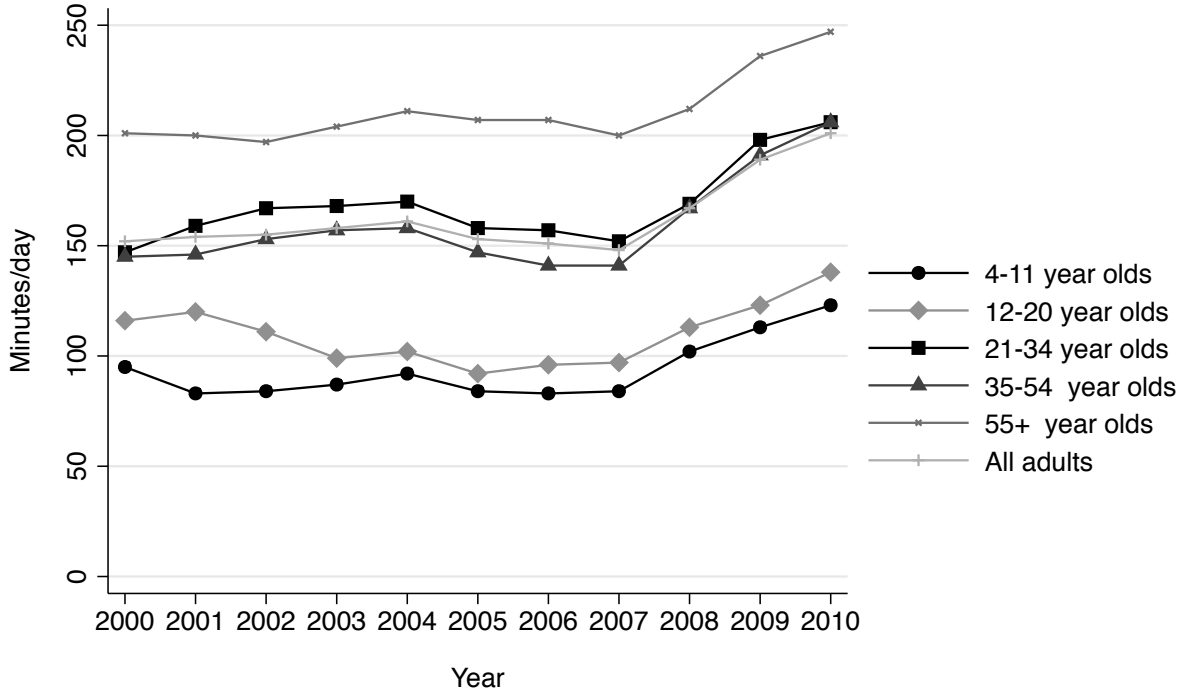

Figure 1. Average TV viewing time (minutes/day) in Denmark from 2000-2010 based on TNS Gallup and DR Medieforskning TV-meter investigations (32).

TV viewing is usually performed in a seated or lying posture and classified as sedentary. Excessive TV viewing on a daily basis could significantly displace time from other activities, especially other sedentary activities and light intensity activities (33, 34). Besides influencing posture (sitting/reclining) and lowering energy expenditure, TV viewing has also been associated with other adverse lifestyle factors. TV viewing may be associated with the intake of foods and beverages that are advertised on TV during and beyond viewing time (35) and could attract some individuals to begin smoking (36). Thus, prolonged TV viewing could influence a number of unhealthy lifestyle behaviors. For all these reasons, and because TV viewing is a very common and pervasive behavior, prolonged viewing time may be an important risk factor for T2D and CVDs, and this particular screen time behavior could have substantial public health impact in all age-groups globally. Thus, quantifying the association of TV viewing with health outcomes is an essential first step for guiding primordial- and primary prevention.

More recently, organizational and national recommendations for sedentary behaviors including screen time for children and adolescents have emerged (37-39). Some of these recommendations state that children and adolescents should limit their recreational screen time to no more than 2 hours per day to minimize health risks (37, 38, 40). The evidence from prospective studies to support these specific time limits is weak, and it is unknown if time spent on TV viewing and computer use each are independently associated with cardiovascular outcomes. Furthermore, the evidence that youth screen time viewing are associated with adult cardiovascular health is scarce (40-42). Thus, further studies on this topic, in particular from prospective observational studies and experimental studies, are likely to increase the confidence that limiting screen time viewing among youth is important for the prevention of adverse health outcomes including cardiovascular risk.

Muscle strengthening activities and muscle strength

The current guidelines for physical activity among children, youth, and adults also include a recommendation to undertake muscle strengthening activity on two or more days/week (adults) or three or more days/week (children and youth) beyond the primary recommendation of 150 min/week (adults) or 60 min/day (children) of aerobic MVPA. While the benefits of resistance exercise in the treatment and management of some diseases and conditions such as osteoporosis, hypertension, and T2D have been documented (43-49) there is currently little evidence to suggest that muscle strengthening activities such as resistance exercise can be beneficial for the prevention of T2D and CVDs. Among adult men, some evidence suggests that low muscle strength is associated with premature mortality independent of cardiorespiratory fitness (50). Other studies among adults have also reported inverse associations of muscle strength with premature mortality and one study with incident T2D, but these have not adjusted their estimates of association for cardiorespiratory fitness (51-55). In children and youth the health benefits of muscle strengthening activity and muscle strength are less clear. A few prior cross-sectional studies among children or adolescents have reported that muscle strength or muscle fitness (composite score based on several strength and endurance tests) is associated with CVD risk factors independent of cardiorespiratory fitness (56, 57). We are not aware of prospective studies examining the influence of muscle strength in childhood or youth on CVD risk factors in adulthood independent of cardiorespiratory fitness. In addition, limited evidence exists from prospective studies examining possible

benefits of engagement in muscle strengthening activity for the prevention of T2D and CVDs in adults.

Summary of introduction, outlines, and aims of the thesis

There are a considerable amount of studies, from both observational and experimental approaches, which suggest participation in aerobic type MVPA and cardiorespiratory fitness are important for the prevention of T2D and CVDs. In contrast, more limited evidence exists from well-conducted studies on the possible benefits of muscle strengthening activities or muscle strength and the possible risk of engagement types of activities that are considered being sedentary for T2D and CVD prevention. The majority of previous observational studies examining the benefits of muscle strength among adults have not adjusted their analyses for cardiorespiratory fitness, and prospective studies in youth are lacking. Thus, any further observational- and experimental studies are essential for our understanding of these types of activities and physical fitness in the prevention of T2D and CVDs. TV viewing is the most common and pervasive sedentary behavior during leisure time in many countries, and national and organizational guidelines for limiting screen time have emerged. However, at the time of the planning of this thesis a systematic and quantitative assessment of published studies on the association of TV viewing and risk of T2D, CVDs, and premature mortality was not available and the evidence from prospective studies that screen time viewing in childhood or youth is associated with adult cardiovascular health is limited.

The overall aims of this thesis were to investigate the associations of different types of physical activities, sedentary activities, and muscle strength with the risk T2D, CVDs, or their biological risk factors in youth and adults. To address these aims we used data from prospective studies conducted among youth and adults. We used data from published prospective studies to quantify an overall estimate of associations of TV viewing with T2D, CVDs, and premature mortality via meta-analyses. We used data from the Danish part of the ongoing prospective cohort study the European Youth Heart Study (EYHS). Furthermore, we used data from the Health Professionals Follow-up Study (HPFS), which is an ongoing prospective cohort study of U.S. male health professionals. The specific aims of the thesis were:

1) To obtain an overall estimate of the association between TV viewing and risk of T2D, CVDs and all-cause mortality from prospective cohort studies and quantify the dose-response relationship of TV viewing with the risk of these adverse health outcomes.
2) To examine the association of TV viewing, computer use, and total leisure screen time viewing in adolescence, and changes in these screen time viewing behaviors, with cardiovascular risk factors in young adulthood among Danish youth participating in the Danish part of the EYHS.
3) To examine the association of weight training with the risk of T2D independent of aerobic physical activity among U.S. men from the HPFS.
4) To examine the association of isometric trunk muscle strength in youth with cardiovascular risk factors in young adulthood independent of cardiorespiratory fitness among Danish youth participating in the Danish part of the EYHS.
5) To examine the independent and combined association of isometric trunk muscle strength and cardiorespiratory fitness in youth with indices of insulin resistance and beta-cell function in young adulthood among Danish youth from EYHS.
6) To examine the association of screen time viewing behaviors with isometric trunk muscle strength independent of cardiorespiratory fitness in a population sample of Danish youth from EYHS.

Materials and methods

The studies in this thesis are all based on observational studies. The first study (I) systematically used all available and published prospective cohort studies to run meta-analyses. The second (II), fourth (IV), and fifth (V) study were all based on an ongoing prospective cohort study among Danish youth sampled in 1997-98 or 2003-04 followed up into young adulthood in 2009-10. The third (III) study was based on an ongoing prospective cohort study of U.S. male health professionals with 18-years of follow-up. The sixth (IV) study was based on the cross-sectional sample among Danish youth conducted in 1997-98 or 2003-04. Table 1 provides an overview of the individual studies.

Study I - Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality: A Meta-analysis

This study was carried out as a meta-analysis with the aim to summarize all published prospective studies to date on the association of TV viewing with the risk of T2D, CVD, and mortality and quantify the dose-response relationship of TV viewing with the risk of these health outcomes.

Study design and data collection

Design and search strategy

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology(58). A systematic search was conducted of the published studies in MEDLINE from 1970 to 01 March 2011 and in EMBASE from 1974 to 01 March 2011.

In addition, reference lists in retrieved articles was examined to identify any studies that were unidentified from the preliminary literature search.

Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria:1) studies that were published in English; 2) studies with a prospective design (cohort-, case-cohort- and nested case-control studies); 3) study population that was healthy at baseline; 4) estimates of relative risk (RR) or odds ratio (OR) with 95% confidence intervals (CI) or reported data to calculate these.

Data extraction

From each retrieved study RR or OR estimates with corresponding 95% CIs were extracted. The aim was to pool risk estimates continuously. If the authors did not report the association with TV viewing as a continuous variable we estimated this using the method of generalized least squares for trend estimation (GLST) described by Orsini et al. (59). For categories of TV viewing that were open (e.g. 4-7 hours/day), we assigned the median values of TV viewing. If the upper bound in the highest category was not provided, we assumed that it had the same amplitude as the preceding category. This procedure was also performed for obtaining data for the dose-response meta-analysis. If the appropriate data were unobtainable, we requested data from the investigators.

Statistical analysis

Estimates of RR were pooled assuming a linear relationship of the natural logarithm of RR with increasing TV viewing time with CIs from each study separately for each outcome using a random-effect meta-analysis. We evaluated statistical heterogeneity of the RRs by calculating the I^2 statistic[11] and publication bias with the use of the Egger test (60). Low, moderate, and high degrees of heterogeneity correspond to I^2 values of 25%, 50%, and 75% respectively. Sensitivity analyses included evaluating whether the results could have been affected markedly by a single study (61), and repeating the analyses using a fixed effect model. We then plotted the possible dose-response relationship based on dose-response meta-analysis (59) using all available data points from each study. To plot the relationship of the natural logarithm of RRs with increasing TV viewing time without assuming linearity and test if they were nonlinear, we added a quadratic term of TV viewing time (changes in model fit were tested by the likelihood ratio test). For any non-linear response, we proceeded using piecewise regression with an inflection point based on the model with the best goodness-of-fit.

Assuming a causal relationship between TV watching and the outcomes and the generalizability of the relationship to the general population, we calculated absolute risk differences (RD) based on the obtained summary estimate and incidence rates from the general US population using the formula: RD=background incidence rate x (RR-1). It should be noted that RD can vary greatly by populations studied and will be greater for high-risk populations (e.g., older age groups) compared to low-risk populations.

Study II - Youth screen-time behaviour is associated with cardiovascular risk in young adulthood: the European Youth Heart Study

This study was done to examine the association of TV viewing, computer use, and total screen time viewing in youth with cardiovascular risk factors in young adulthood and, furthermore, examine the influence of changes in viewing time on later cardiovascular risk.

Design, study population and assessment of exposure and outcomes

Design and study population

The study was based on the Danish part of the EYHS; an international population-based multicenter study that addresses cardiovascular disease (CVD) risk factors in children and adolescents. In this study a random sample of 658 15-year old adolescents were invited to participate in 1997-98, of whom 429 (65%) agreed to take part in the study. In 2003-04 another random sample of 771 15-year old adolescents was invited of whom 444 (58%) agreed to take part. In 2009-10 a 6- or 12 year follow-up was conducted where all originally invited participants from 1997-98 and 2003-04 were invited again. The eligible cohort for the current analyses was n=435 individuals who had complete data on exposures and outcomes (244 individuals with 6-year follow-up and 191 individuals with 12-year follow-up). The study was approved by the local scientific ethics committee and all participants gave informed consent to participate.

Television, computer use, and total screen time viewing

At baseline and follow-up, TV and computer use during leisure was obtained by self-report. In both instances this was done using a computer-based questionnaire. At baseline, two questions were asked about the amount of time viewing TV (before and after school). From these two questions a summary variable of the daily amount of TV viewing in adolescence was constructed (hours/day). Frequency of eating while viewing TV (five-point scale) was also asked. Daily time spent using computer in adolescence was asked in one question. At follow-up the participants were asked to report their amount of TV viewing time (hours and minutes) in the morning, afternoon, and evening. Again, a summary variable for daily TV viewing (hours/day) in young adulthood was constructed. Participants were asked about their time spent using a computer during leisure time (hours/day and min/day) separately for surfing the internet, playing games, and other tasks (i.e. word processing). From response to these questions a summary variable for

daily computer usage was constructed (hours/day). A total screen time variable (hours/day) was created by summarizing TV and computer use in adolescence and young adulthood, respectively. The specific screen time viewing questions used at baseline or follow-up have not been directly validated, however, previous methodological evaluations of similar questions have shown moderate to high reliability and moderate validity against a diary as a criterion measure among both youth and adults (62, 63). Furthermore, a previous report from EYHS shows that the TV viewing time question demonstrate convergent validity in that it has been associated with TV home environment factors such as whether the TV was on when the adolescent returned home (64).

Assessment of other covariates

Monthly frequency of soft drinks, fruit, and vegetable intake, and smoking status were obtained by self-report in adolescence. Family history of CVD (paternal or maternal, yes/no) and parental educational level were obtained by parental self-report. Parental educational status was defined according to the International Standard Classification of Education (ISCED) (UNESCO 1997). However, as the details obtained of the description of education were insufficient, the ISCED seven point scale was combined in 3 new groups: I=basic education (level 1-2); II=secondary or post-secondary education (level 3-4); and III=tertiary education (level 5-7). MVPA and sedentary time in adolescence was assessed using accelerometry. An output >2000 counts/min (equivalent to walking about 4 km/h) was defined as MVPA and an output <100 count/min was defined as sedentary. MVPA and sedentary time were expressed as continuous variables as percentage of total registered time.

Cardiovascular risk factors

Height, weight, and waist circumference (WC) were measured using standard anthropometric procedures. Fasting blood samples (overnight) were taken in the morning from the antecubital vein. Samples were aliquoted and separated within 30 min, and then stored at −80 °C until they were transported to a WHO-certified laboratory in Bristol and Cambridge (UK), for analysis at baseline and in Cambridge at follow-up. Samples were analyzed for serum glucose, insulin, HDL cholesterol, and triglyceride using standard enzymatic immunoassay methods. Between-laboratory correlations in lipids, glucose, and insulin for 30 randomly selected samples analyzed at both laboratories were 0.94–0.98 at baseline (65).

Resting BP was measured with a Dinamap paediatric and adult neonatal vital signs monitor (model XL, Critikron, Inc, Tampa, FL, USA) using an appropriate cuff size. Five measurements were taken at 2-min intervals with the mean of the final three measurements used in all analyses. Prior to measurements individuals were resting for five minutes while seated.

A continuous metabolic syndrome z-score was calculated to preserve statistical power and because the number of incident cases of metabolic syndrome according to the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) definition (66) in young adulthood was low (n=17). The z-score was based on the AHA/NHLBI definition with additional inclusion of fasting insulin. Thus, WC, the mean of diastolic and systolic BP, triglycerides, HDL (inverted), fasting glucose, and fasting insulin were standardized and subsequently summed to create a continuous metabolic syndrome z-score. Standardization in young adulthood (follow up) was done according to the baseline distribution (mean and SD) of each risk factor.

Statistical analysis

Associations of screen time use in adolescence with cardiovascular risk factors in young adulthood were analyzed using multiple linear regression with baseline levels of respective risk factors included as a covariate. In multivariable analyses we adjusted for parental educational level, current smoking, family history of CVD, frequency of intake of soft drinks, intake of fruit and vegetables, and MVPA. To examine whether the association of prolonged TV viewing with metabolic risk may be mediated by adiposity, we also analyzed the association of screen time viewing with metabolic syndrome z-score without adiposity included but with adjustment for WC in adolescence. Because adiposity also have been shown to predict sedentary time (67), we also analyzed if BMI and WC in adolescence was associated with screen time viewing in young adulthood.

To analyze the association of change in viewing time with each respective cardiovascular risk factor in young adulthood, we used the difference in young adult- and adolescence viewing time as a continuous variable adjusting for adolescence viewing time, and in addition analyzed change in TV viewing and total screen time viewing as categorical variables using the following categories: stable or decrease (≤0 hours/day), modest increase (>0-2 hours/day), large increase (>2 hours/day). A test for linear trend across groups of change in the categorical analysis was done by treating the 'change variable' as ordinal in the models.

As information on accelerometry measured MVPA and sedentary behavior at baseline was missing among 161 individuals (37%), we imputed missing values using a multiple univariate linear regression imputation approach ("mi impute" in STATA) including all covariates. Beta coefficients and SE's were obtained based on 20 imputed datasets while the variability between imputations is adjusted for (68).

Study III – A Prospective Study of Weight Training and Risk of Type 2 Diabetes Mellitus in Men

This study was carried out to examine the association of weight training with the risk of T2D independent of aerobic physical activity among men followed biennially for 18 years in the HPFS.

Design, study population and assessment of exposure and outcomes

Design and study population

The HPFS is an ongoing prospective cohort study of 51,529 male health professionals (dentists, optometrists, pharmacists, podiatrists, osteopaths, and veterinarians) aged 40 to 75 years at baseline in 1986. Every two years the cohort participants are sent a questionnaire on diseases and personal- and lifestyle characteristics such as height, weight, smoking status, dietary intake (food frequency questionnaire (FFQ)), and physical activity. For this analysis we excluded those men who reported a history of diabetes, cancer, myocardial infarction, angina, coronary artery bypass graft, other heart conditions, stroke, or pulmonary embolism on the baseline questionnaire (1986) and in 1988, and 1990, leaving a study population of 32,002 participants free of major chronic disease and with information on exposures and covariates. The Harvard School of Public Health Institutional Review Board approved the study.

Assessment of weight training, other physical activity and TV viewing

From 1990 and every other year through 2006, the participants reported their average weekly amount of weight training, other physical activities, and TV viewing. Other physical activities included walking, jogging, running, bicycling, swimming, tennis, squash, calisthenics/rowing, and heavy outdoor work. There were 13 response categories ranging from none to >40 hours/week for weight training and other activities. Participants were also asked about the daily number of flights of stairs climbed, and

usual walking pace. Of these other physical activities brisk walking, jogging, running, bicycling, swimming, tennis, squash, calisthenics/rowing was considered aerobic physical activity of at least moderate intensity (≥3 METs). These activities were used because they are often performed repetitively and produce dynamic contractions of large muscle groups for an extended period of time (24). The total time spent on aerobic exercise of at least moderate intensity (≥3 METs) were calculated and subsequently participants were grouped into four categories: none, 1-59, 60-149, and ≥150 min/week. The same categories were used for weight training. A variable representing unstructured activity of at least moderate intensity consisting of MET-hours per week of heavy outdoor work and stair climbing was also constructed (69). The reproducibility and validity of the PA questionnaire have been assessed in a sub-sample of the HPFS participants. The Pearson correlation between PA of vigorous intensity from diaries for 4 weeks across different seasons and that from the questionnaire was 0.58 and for weight training, the correlation was 0.79 (70). Reproducibility of vigorous physical activities and weight training from two questionnaires were 0.52 and 0.50 respectively. Another study has reported a correlation of 0.54 between PA score obtained from a similar questionnaire and maximum oxygen uptake (71).

Assessment of type 2 diabetes and death

In HPFS T2D is assessed by self-report. In our study this included cases of T2D that occurred between return of the questionnaire in 1990 and January 31 in 2008. Men who reported a diagnosis of diabetes in the biannual follow-up questionnaires were sent a supplementary questionnaire to confirm the diagnosis obtaining information on symptoms, treatment, and diagnostic tests. From 1990 to 1996 the criteria from the National Diabetes Data Group was used to confirm self-reported diagnosis of T2D. In this period a case of T2D was considered confirmed if at least 1 of the following was reported on the supplementary questionnaire: (1) 1 or more classic symptoms (excessive thirst, polyuria, weight loss, hunger) plus 1 fasting plasma glucose level of at least 7.8 mmol/L (140 mg/dL) or random plasma glucose of at least 11.1 mmol/L (200 mg/dL); (2) at least 2 elevated plasma glucose concentrations on different occasions (fasting, ≥7.8 mmol/L; random, ≥11.1 mmol/L; and/or ≥11.1 mmol/L after ≥2 hours of oral glucose tolerance testing) in the absence of symptoms; or (3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). From 1998 we used the American Diabetes Association criteria. The diagnostic criteria changed in June 1998, and fasting plasma

glucose of 7.0 mmol/l was now considered the threshold for the diagnosis of diabetes instead of 7.8 mmol/l. The assessment of T2D by self-reported was evaluated in a validation study among a sub-sample of HPFS participants. In this validation study 97% (57 of 59) of self-reported T2D cases were confirmed by means of medical record review.

Deaths at or before baseline and during follow-up were identified by searching the National Death Index, next of kin or from postal authorities. Death due to CVDs was classified using International Classification of Diseases (eighth revision). The National Death Index has an estimated sensitivity of at least 98%, meaning that most deaths are correctly identified (72).

Assessment of other covariates

Family history of T2D was assessed at baseline by self-report. Smoking status and BMI were assessed at baseline and biannually thereafter. Dietary factors were assessed in 1990, 1994, 1998, 2002, and 2006 using a 131- item validated FFQ (73). Daily intake of total energy (cal/d), saturated fat to polyunsaturated fat ratio, trans fat (% of total energy), alcohol intake, coffee intake, cereal fiber (g/d), whole grains (g/d), and glycemic load were considered as covariates in the analyses as these are putative dietary risk factors for T2D (74).

Statistical analysis

Person-time at risk was calculated from the return of the 1990 questionnaire until January 31 2008, death, loss to follow-up, or whichever occurred first. Relative risks (RRs) of T2D by categories of weight training and aerobic exercise were estimated using time dependent cox proportional-hazard regression. To control for calendar time and age the analyses were stratified jointly by age (in months) at start of follow-up and the year of questionnaire return. We calculated cumulative averages of weight training and aerobic activity from baseline (1990) to censoring time to minimize measurement error and to characterize long term exposure status. In multivariable analysis we additionally adjusted for aerobic activity, other physical activity, TV viewing, alcohol intake, coffee intake, smoking, ethnicity, family history of diabetes, and the dietary variables total calorie intake, saturated fat to polyunsaturated fat ratio, trans fat, cereal fiber, whole grains, and glycemic load. Tests for trend were performed by assigning the median value of each category of the exposure and treating this variable as continuous. To examine the combined association of weight training and aerobic activity, we constructed a joint

variable of weight training (4 categories) and aerobic activity (2 categories representing adherence to current recommendations) and associated that with T2D risk.

We also examined the nature of the possible dose-response relationship between weight training and T2DM by using restricted cubic spline regression with 4 knots (75). Deviation from linearity was tested using the likelihood ratio test by comparing models with cubic spline terms and models only containing the linear term.

We performed several sensitivity analyses to assess the robustness of the results. Firstly, we used the simple update- and the baseline information respectively on weight training as an alternative for the cumulative average. Secondly, we performed an analysis using a 4-year lag in exposure classification to assess the possibility of reverse causality. Thirdly, we included confounding variables assessed on the continuous scale in this form in the models to address the possibility of residual confounding. Finally, because in theory, individuals may die before they have the chance to develop T2D we repeated the analysis with death from all causes treated as a competing risk according to the method of Fine and Gray (76).

Study IV and V – Association of muscle strength in youth with cardiovascular risk and insulin resistance and beta-cell function in young adulthood (The European Youth Heart Study)

Study IV was performed to examine the association of isometric trunk muscle strength in youth with cardiovascular risk factors in young adulthood independent of cardiorespiratory fitness. Study V was carried out to examine the independent and combined association of isometric trunk muscle strength and cardiovascular fitness in youth with insulin resistance and beta-cell function in young adulthood.

Design, study population and assessment of exposure and outcomes

Design and study population

This study was based on the Danish part of the EYHS as previously described in study II. Isometric muscle strength was assessed in a sub-group of 243 participants in 1997-98, whereas virtually all (n=441) participants had muscle strength evaluated in 2003-04. The eligible individuals for study IV were n=332 individuals who had complete data on all exposure and outcome variables. For study V, n=317 had complete data on all exposure and outcome variables.

Muscle strength

Isometric muscle strength was obtained during maximal voluntary contraction (MVC) of abdominal and back muscles. The participants were standing upright and positioned with a strap around the shoulders connected to a strain-gauge dynamometer (77). Assessment of abdominal strength was performed with the back against the dynamometer performing maximal forward flexion. For MVC of the low back muscles, the participants were positioned with the front against the dynamometer performing maximal backward extension. Isometric muscle strength was calculated as the mean of abdominal- and back strength (Newton (N)) divided by body weight (N/kg). A previous study among adults have reported high reliability of these particular isometric strength measures (intraclass correlation coefficient>0.9) (78).

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed during a progressive maximal ergometer bicycle test (Ergomedic 839; Monark, Varberg, Sweden). Heart rate (HR) was recorded every 5 s throughout the test using a HR monitor (Polar Vantage, Finland). Criteria for a maximal effort were HR of 185 beats per minute or greater, and a subjective judgment by the observer that the participant could no longer continue, even after encouragement. Maximal power output (wattmax) from the test was used to estimate maximal oxygen uptake using the following equation VO_2-max ($ml \cdot min^{-1}$) = 0.465+(0.0112*wattmax)+(0.172*sex), where sex is boys=1 and girls=0 (79). The fitness test is highly reproducible (coefficient of variation 2.5-4.8%) and a previous validation study in 15-year olds have shown that this measure is highly correlated with VO_2-max assessed directly (r>0.90, P<0.001) (80).

Other covariates

Information on TV viewing, parental educational level, smoking, family history of CVD, frequency of intake of soft drinks, and intake of fruit and vegetables in youth were considered confounding factors and the assessment of these are described in study II.

Cardiovascular risk factors

Waist circumference, BMI, systolic- and diastolic BP, and fasting serum levels of HDL, triglyceride, and glucose were assessed at baseline in youth and at follow-up in young

adulthood as described in study II. A continuous composite CVD risk z-score using components of the metabolic syndrome suggested by the AHA and the NHLBI was calculated (66). Furthermore, abdominal obesity, raised BP, raised triglycerides, low HDL, and raised fasting plasma glucose were defined according to Third Report of the NCEP Adult Treatment Panel III (81).

Insulin resistance and beta-cell function

The homeostasis model assessment of insulin resistance (HOMA-IR=(fasting glucose (mmol/l) x insulin (μU/ml))/ 22.5) and β-cell function (HOMA-B=(insulin (μU/ml) x 20)/(glucose (mmol/l)-3.5) were used to quantify the level of insulin resistance and secretion (82). Both these measures have been validated as indices of insulin resistance and pancreatic beta-cell function in healthy adolescents (83).

Statistical analysis

The association of muscle strength in adolescence with cardiovascular risk factors, HOMA-IR, and HOMA-B in young adulthood was analyzed using multiple linear regression with baseline levels of respective risk factors included as a covariate. Firstly, an analysis was carried out adjusting for age at baseline, follow-up time, sex, and recruitment period. Further adjustments were done for for baseline information on TV viewing, parental educational level, smoking, family history of CVD (or T2D in analyses with HOMA-IR and HOMA-B as outcomes), frequency of intake of soft drinks, and intake of fruit and vegetables. A subsequent model was fitted adjusting for cardiorespiratory fitness, and a fully adjusted model also included BMI or WC. Values of insulin, HOMA-IR, and HOMA-B were natural log transformed. Thus, regression coefficients from these models were exponentiated to give ratios of geometric means (expressed in percent) per SD difference in exposure.

The associations of muscle strength with the odds of incident general overweight or obesity, abdominal obesity, raised BP, raised triglyceride, and low HDL were analyzed using multiple logistic regression adjusting for the same covariates as in the linear models. Prevalent cases of each respective risk factor at baseline were excluded in these models. As the number of incident cases for some of the outcomes was low (e.g. n=24 for raised BP) we performed a sensitivity analysis using propensity score matching (84) to comply with the '≥10 outcome events per covariate' assumption including the same confounders as in the multivariable adjusted models. Multiple logistic regression

was also used to analyze the association of muscle strength with the odds of insulin resistance, defined as HOMA-IR value above the 75th percentile in young adulthood (18).

Because of missing data and loss to follow-up a sensitivity analyses was carried out comparing estimates of associations in the sample with complete data on covariates and outcomes (n=332 or n=317) with the full sample (n=873) with missing values being imputed. Missing values were imputed using a multiple chained equation imputation approach ("mi impute chained" in STATA) including all covariates and respective outcomes and beta coefficients and SE's were obtained based on 20 imputed datasets (85, 86). Multiple imputation works by using the distribution of the observed data to estimate a set of plausible values for the missing data while incorporating random components to reflect uncertainty (86). Multiple data sets are created and then analyzed individually, and in turn combined to obtain the overall estimates with confidence intervals.

Study VI – Screen time viewing behaviors and trunk muscle strength in a population sample of Danish youth from The European Youth Heart Study

This study examined the association of screen time viewing behaviors with abdominal and back isometric strength independent of cardiorespiratory fitness in a population sample of Danish adolescents.

Design, study population and assessment of exposure and outcomes

Design and study population

This study was cross-sectional based on the Danish part of the EYHS as previously described in study II. For this particular study the eligible participants were adolescents who had isometric trunk muscle strength assessed in 1997-98 or 2003-04. As described in study IV and V, n=684 of n=873 sampled adolescents had isometric muscle strength assessed. Of these n=606 had full data on relevant exposures and confounders.

Muscle strength and cardiorespiratory fitness

See study IV and V for a detailed description on the assessment and expression of these outcomes.

Television, computer use, total screen time viewing, and covariates

Assessment and expression of screen time viewing behaviors, and the following covariates; parental educational level, smoking, family history of CVD, frequency of intake of soft drinks, intake of fruit and vegetables, and acclerometry measured MVPA in youth that were considered confounding factors are described in study II.

Statistical analysis

Associations of TV viewing, computer use, and total screen time viewing with isometric trunk muscle strength were analyzed using multivariable adjusted linear regression. Initially, models were adjusted for age, sex, recruitment period, parental educational status, smoking status, intake of soft drinks, and fruit- and vegetable intake. Then analyses with additional adjustment for CRF and waist circumference were carried out. Finally, a multivariable adjusted model including both TV viewing and computer use in the same model was run to assess whether both types of viewing behavior, independent of each other, were associated with trunk muscle strength. It was also examined whether the association of screen time viewing with trunk muscle strength differed by CRF level, parental educational level, and sex. In sensitivity analysis we also additionally adjusted for objectively measured MVPA from accelerometry to examine if any residual confounding by physical activity remained that CRF may not have captured. Because 37% of the participants with otherwise full data were missing on accelerometer measured MVPA, we imputed missing values on MVPA using a multiple univariate linear regression imputation approach ("mi impute" in STATA) including all covariates and the outcome. We obtained beta coefficients and SE's based on 20 imputed datasets while the variability between imputations is adjusted for.

Table 1. Overview of study designs, period of data collection, study population, exposures, outcomes, sample sizes, and data-analysis of studies included in the thesis.

	Study design, period, and population	Exposures	Outcomes	Sample size (n)	Data analysis
Study I	Meta-analysis of prospective cohort studies 1982-2009 North American, European, Australian men and women	TV viewing	T2D Fatal- and non-fatal CVDs Mortality from all-causes	T2D: 175,938 (1.1 million PY) CVD: 34,253 Mortality: 26,509 (202,353 PY)	Random effect meta-analysis
Study II	Prospective cohort 1997-2010 Danish youth (14-16-years) followed into young adulthood (21- or 27 years of age)	TV viewing Computer use Total screen time viewing	BMI, waist circumference, blood pressure, triglyceride, HDL-C, glucose, insulin, composite CVD risk score	435	Multiple linear regression analysis
Study III	Prospective cohort 1990-2008 US men ≥ 44-79 years of age (health professionals)	Weight training Aerobic physical activity	T2D	32,002 (508,332 PY)	Cox proportional hazard regression
Study IV	Prospective cohort 1997-2010 Danish youth (14-16-years) followed into young adulthood (21- or 27 years of age)	Isometric muscle strength	BMI, waist circumference, blood pressure, triglyceride, HDL-C, glucose, composite CVD risk score	332	Multiple linear and logistic regression analysis
Study V	Prospective cohort 1997-2010 Danish youth (14-16-years) followed into young adulthood (21- or 27 years of age)	Isometric muscle strength Cardiorespiratory fitness	Insulin resistance (HOMA-IR), beta-cell function (HOMA-B)	317	Multiple linear regression analysis
Study VI	Cross-sectional study 1997-2003 Danish youth (14-16-years)	TV viewing Computer use Total screen time viewing	Isometric muscle strength	606	Multiple linear regression analysis

TV=television, T2D=type 2 diabetes, CVD=cardiovascular disease, BMI=body mass index, HDL-C=high density lipoprotein cholesterol, PY=person-years.

Results

The main findings of the individual studies I-VI are described in the section below. For a more detailed description of the results from each individual study please see appendences I-VI.

Study I

We retrieved 1655 studies from our preliminary search. Of these, 12 articles were identified for further full review (some reported analyses on more than one relevant outcome): 4 reports on T2D, 8 reports on CVD, and 4 reports on all-cause mortality. After full review 8 studies in total were included: 4 reports on T2D (total of 175,938 individuals, 6,428 cases during 1,113,289 person-years), 4 report on CVD (total of 34,253 individuals, 1,052 cases), and 3 reports on mortality of all-causes (total of 26,509 individuals, 1,879 cases during 182,989 person-years). The mean follow-up duration was 8.5 (1.9), 10.4 (7.4), and 6.8 (2.6) years for T2D, CVD, and all-cause mortality respectively. Although, the number of potential confounding factors included in the multivariable adjusted model varied between studies, these were fairly homogeneous with respect to type and quality. That is, all included studies were well-established prospective cohort studies of high quality; relatively large samples, adequate follow-up time, outcome assessment from registry or highly accurate measure of self report, exclusion of diseased participants at baseline, and well performed statistical analyses with adjustment for relevant putative confounding factors.

The pooled RRs per two hours TV-viewing/day were 1.20 [95% CI 1.14-1.27], 1.15 [95% CI: 1.06-1.23], and 1.13 [95% CI 1.07-1.18] for T2D, CVD, and mortality from all-causes respectively. While the associations between time spent on TV viewing and risk of T2D and CVD were linear, the risk of all-cause mortality appeared to increase with TV viewing time above 3 hours/day (p=0.007 for a non-linear dose-response relationship). In piecewise regression analysis, we obtained the best fit an inflection point at 3 hours TV viewing/day (p=0.01 for difference in slopes). Up to 3 hours/day there was no association of TV viewing whereas above 3 hours/day the RR was 1.30 [95% CI 1.06-1.56] per two hours TV viewing/day. The estimated absolute risk differences (cases per 100,000 individuals/year) per 2 hours TV viewing/day were 176, 38, and 104 for T2D, CVD and mortality, respectively (based on the most recent U.S. diabetes incidence statistics (87), American Heart Association (AHA) U.S. CVD mortality rate statistics (88),

and the US total mortality rate statistics (89)). In all analyses there were low or moderate statistical heterogeneity between studies and we observed no evidence of publication bias based on Egger's asymmetry test. The summary estimates were very consistent when repeating analyses using a fixed-effects model and omitting one study at a time and recalculating the pooled RRs for the remainder of the studies showed that none of the individual studies substantially influenced the pooled RR for either outcome.

Study II

After adjustment for parental educational level, smoking, family history of CVD, frequency of intake of soft drinks, intake of fruit and vegetables, and MVPA each 1 hour difference in TV viewing time in adolescence was associated with the 0.24 kg/m^2 [95%CI 0.00–0.49] BMI points, 0.83 cm [95%CI 0.13–1.53] WC, 0.05 mmol/l [95%CI 0.01–1.10] triglyceride level, 2.00 pmol/l [95%CI −0.19–4.17] insulin, and 0.45 SD [95%CI 0.14–0.76] metabolic syndrome z-score in young adulthood. Slightly weaker associations were observed for total screen time viewing with these outcomes. In multivariable adjusted analyses total screen time viewing were significantly associated with BMI, WC, triglycerides, and metabolic syndrome z-score. Individuals who increased their TV, computer, or total viewing time with more than 2 hours/day from adolescence to young adulthood had 0.90 [95%CI 0.12–1.69], 0.95 [95%CI 0.01–1.88], 1.40 [95%CI 0.28–2.51] higher BMI respectively in young adulthood compared with individuals who remained stable or decreased their viewing time. Furthermore, plasma insulin and metabolic syndrome z-scores were also higher among individuals who increased their TV, computer, or total viewing time respectively with more than 2 hours/day compared with individuals who remained stable or decreased their viewing time ($p<0.05$). Including change in TV viewing and computer use in the same model, changes in both types of viewing were independently associated with BMI and insulin in multivariable-adjusted analyses.

Study III

During 508,332 person years of follow-up (18 years), 2,278 new cases of T2D were documented. In multivariable adjusted analysis including aerobic physical activity, men performing weight training 1–59, 60–149, and ≥150 min/week had RRs of 0.88, 0,75, and 0.66 lower risk of T2D ($p<0.001$ for trend), respectively, compared to men reporting

no weight training. The RR for T2D for men performing 1-59, 60-149, and ≥150 min/week of aerobic exercise respectively compared to men reporting no aerobic exercise was 0.93, 0.69, and 0.48 ($p<0.001$ for trend) in multivariable adjusted analysis. The joint association of weight training and aerobic exercise with the risk of T2D revealed no indication of multiplicative interaction ($p=0.26$) and men who adhered to the current recommendations on aerobic exercise (at least 150 min/week) and engaged in weight training of at least 150 min/week had the greatest reduction in T2D risk (RR=0.41, 95%CI 0.27-0.61). These results were robust to a number of sensitivity analyses including using simple update- and the baseline information respectively on weight training as an alternative for the cumulative average, restricting the analyses to men reporting no aerobic activity, and using a 4-year lag analyses in exposure classification. In a secondary analyses weight training was associated with mortality from CVD- and all causes in age-adjusted analyses, but these associations were attenuated in multivariable adjusted analyses.

Study IV

Muscle strength in youth was significantly associated with BMI, WC, triglyceride, HDL-C, DBP, and composite CVD risk factor score in young adulthood in age, follow-up time, sex, and recruitment period adjusted analyses. In analyses with further adjustment for TV-viewing, parental education level, smoking status, intake of soft drinks, fruit- and vegetable intake, family history of CVD, and cardiorespiratory fitness each 1 SD of muscle strength in youth (0.17 N/kg) were inversely associated with BMI (-0.60 kg/m^2, 95%CI -0.97;-0.22), triglyceride (-0.09 mmol/l, 95%CI -0.16;-0.02), diastolic BP (-1.22 mmHg, 95%CI -2.15;-0.29), and a composite cardiovascular risk factor score (-0.61 SD, 95%CI -1.03;-0.20) in young adulthood. Associations to triglyceride, diastolic BP, and the cardiovascular risk factor score remained with additional adjustment for waist circumference or BMI. During an average of 8 years of follow-up from adolescence, 82, 32, 24, 36, and 55 number of incident cases of general overweight or obesity, abdominal obesity, raised BP, raised triglyceride levels, low HDL-C respectively occurred in young adulthood. In multivariable adjusted analyses including cardiorespiratory fitness, each 1 SD of muscle strength was significantly associated with 0.59 [95%CI 0.40;0.87] lower odds of general overweight/obesity in young adulthood ($p=0.007$) and were marginally associated with incident raised BP, raised triglyceride, and low HDL-C. Results from the sensitivity analysis comparing associations based on non-imputed samples (n=332) with

imputed samples that were missing due to loss-to follow-up or missing information on relevant data were fairly similar.

Study V

Isometric trunk muscle strength and cardiorespiratory fitness in youth were both significantly inversely associated with fasting insulin, HOMA-IR, and HOMA-B in young adulthood in multivariable adjusted analyses. Trunk muscle strength was also inversely associated with fasting glucose, however, this analysis was not significant. For each 1 SD difference in isometric muscle strength (0.16 N/kg) in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed with -11.3% [95%CI -17.0;-5.2], -12.2% [95%CI -18.2;-5.7], and -8.9% [95%CI -14.4;-3.0] respectively in young adulthood following adjustment for cardiorespiratory fitness and personal- lifestyle and demographic factors. Results for cardiorespiratory fitness were very similar in magnitude and the magnitude of associations for both exposures were unchanged with additional adjustment for general or abdominal adiposity in youth. When repeating these analyses based on imputed samples (n=873) associations were essentially similar to the non-imputed analyses. In logistic models each 1 SD difference in muscle strength (0.16 N/kg) and cardiorespiratory fitness (6.8 ml O_2/min/kg) in youth were significantly associated with 0.56 [95% CI 0.39-0.81] and 0.63 [95% CI 0.43-0.94] lower odds of adverse levels of HOMA-IR in young adulthood respectively. The combined associations of muscle strength and cardiorespiratory fitness with fasting insulin, HOMA-IR, and HOMA-B were additive ($p>0.25$ for multiplicative interaction on all outcomes) and adolescents being in the highest sex-specific tertile of both isometric muscle strength and cardiorespiratory fitness had the lowest levels of these glucose metabolism outcomes.

Study VI

Prolonged TV viewing, computer use, and total screen time use were inversely associated with trunk muscle strength in analyses adjusting for age, sex, recruitment period, parental education level, smoking status, intake of soft drinks, fruit- and vegetable intake, family history of CVD. After further adjustment for cardiorespiratory fitness, and subsequently waist circumference, associations remained for computer use and total screen time but TV viewing were only marginally associated with muscle strength after these additional adjustments (-0.05 SD [95%CI -0.11;0.005] muscle strength per 1

hours/day difference in TV viewing time, p=0.08). Each 1 hour/day difference in total screen time use was associated with -0.09 SD [95%CI -0.14;-0.04] lower trunk muscle strength in the fully adjusted model (p=0.001). There were no indications that the association of screen time use with trunk muscle strength was attenuated among highly fit individuals (P=0.91 for cardiorespiratory fitness by screen time interaction on trunk muscle strength). Furthermore, sensitivity analysis did not suggest that the association of screen time use with trunk muscle strength was confounded by MVPA.

Discussion

The studies in this thesis were all based on data collected in observational studies. The next sections discuss the methodological considerations to the studies carried out, including selection bias, information bias, confounding, reverse causation bias, and generalizability. It also discusses the main findings in relation to other studies and the possible biological mechanism underlying the observed associations.

Methodological considerations to the studies

Bias in the meta-analysis (study I)

The results of the meta-analysis of prospective cohort studies can be biased in a number of ways. Firstly, the meta-analysis was restricted to available studies and their inherent limitations. Thus, each estimate retrieved from the included studies could be biased due to selection bias, information bias, and confounding. The included studies were based on fairly large samples, had adequate follow-up time, excluded diseased participants at baseline, and the statistical analyses were generally well carried out with adjustment for major confounding factors. The assessment of TV viewing time was based on self-report in all studies, and only three studies obtained information on viewing time during follow-up. Thus, estimates may have been underestimated due to random error (see the section on information bias later). Since all individuals were free of major chronic disease at baseline, we do not expect that errors in TV viewing time assessment are differentially related to the likelihood of getting the outcome. Incomplete retrieval of included studies can also cause bias, however, two researchers extracted data and any disagreements were resolved by consensus, which should limit this possibility. Because the meta-analysis was based on a relatively small number of studies, there is still a possibility of publication bias, considering that the tests we undertook to evaluate this were likely to be underpowered. The number of studies also limited the ability to determine whether heterogeneity in summary estimates was explained by factors related to study characteristics and quality. This could include study location, years of follow-up, properties of the assessment of TV viewing, CVD disease outcome (fatal, non fatal CVD, coronary heart disease, stroke), degree of covariate adjustment (most studies adjusted for major determinant of diseases), and overall study quality.

Selection bias

In the prospective analyses based on EYHS data in study II, IV, and V a considerable number of individuals were either lost to follow-up or had missing data for some variables and attrition analyses indicated that data was not missing completely at random. If the likelihood of a particular value being missing does not depend on the observed data (or other unmeasured characteristics), the data are completely missing at random and a complete-case analysis will not be affected by selection bias. If however, the likelihood of a particular value being missing depends on the observed data and also on other unmeasured characteristics, then the data is either missing at random or not missing at random respectively. In these cases estimates of association from a complete-case analyses may be affected by selection bias, i.e. association between exposure and outcome among those included in the analysis differs from the association among those eligible. If data is either missing at random or not missing at random multiple imputation may be used to give an indication of possible selection bias in complete-case analyses. We therefore ran multiple imputation analyses by chained equations (86) (no assumption on missing data pattern) using all available data to compare estimates from these analyses with estimates from complete-case analyses to quantitatively assess the possibility of selection bias. We did not see indications that these estimates differed which gives us confidence that our results were unaffected by selection bias. In study III, which was based on a large sample of U.S. health professionals, a very high participation rate was accomplished and all participants at baseline were free of chronic disease (including T2D) and the possibility of selection bias are less likely. The analysis in study VI was based on cross-sectional data, which can be more vulnerable to selection bias if participants are aware of the study question, however, this is very unlikely in this study. The attrition analysis in study VI did not indicate problems with selection bias as the majority of characteristics appeared similar between included individuals and individuals with missing data (missing data were on muscle strength in particular).

Information bias

In study I, II, III, and VI the exposures were all self-reported time spent in types of physical activities, and some degree of random measurement error is inevitable. Random measurement error (non-differential) in exposure classification causes regression dilution bias in association analyses and is usually impossible to rule out, especially when lifestyle

factors are exposure variables. In the prospective studies (I, II, and III), the exposure classification was done before the outcome assessments and recall bias (differential) is therefore less likely to be of concern. In study III exposure assessments (i.e. weight training) were carried out biannually during 18 years of follow-up and as a consequence random errors are significantly reduced and less of a problem compared with cohort studies using only baseline assessment of exposures. TV viewing time or screen time were exposures in study I, II, and IV. Reliability of self-reported screen use among adolescents and adults has been reported moderate to excellent (62, 90-93). It is difficult to validate screen time use with an objective criterion measure, as these behaviors are type specific. Previous studies have evaluated questionnaire reported screen time use against diary as the criterion measure and validity has been reported moderate (92, 93). Because excessive screen time use may be regarded undesirable by many individuals, underestimation of these behaviors may be likely, however, if the degree of underestimation is unrelated to outcome status it will not cause differential bias. The exposure in the prospective studies IV and V was objectively assessed trunk muscle strength using a highly reliable method of assessment, and it is unlikely that error in this measure have caused differential bias in estimates of association.

Random measurement error in variables included in regression models as confounding factors can lead to both over- and underestimation of the estimate of association. Considering that many confounding factors in the analyses of all studies in this thesis were lifestyle factors we cannot exclude the possibility that associations were either over- or underestimated due to imperfect assessment of these variables (equivalent to residual confounding which is discussed in the next paragraph).

Errors in the assessment of outcomes in all studies included in this thesis were unlikely to be related to exposure status. In study I and III some outcomes were self-reported, however, these were performed after exposure assessment and recall bias is less likely. Although the error in the self-reported T2D outcome in study III and in all included studies in the meta-analysis of T2D may be non-differentially with respect to exposure status (weight training or TV-viewing), undiagnosed T2D may lead to underestimation of associations. Furthermore, if undiagnosed T2D is more common among individuals reporting more TV or engage in less weight training a further underestimation of the association may occur. In study II, IV, V, and VI outcomes (biological risk factors or trunk muscle strength) were objectively assessed and therefore

blinded regarding information on exposure status and any error in these assessments are likely to be non-differentially related to exposure status.

In study V HOMA-IR and HOMA-B index were used to quantify the level of insulin resistance and secretion respectively (82). Although both these measures have been validated as indices of insulin resistance and pancreatic beta-cell function in healthy adolescents and among adults (83, 94, 95), the correlation between insulin resistance derived from the euglycemic-hyperinsulinemic- and hyperglycemic clamp, which is the gold standards for assessing insulin resistance and secretion respectively, is only modest. In the largest study to date comparing estimates of insulin resistance from HOMA-IR with the clamp among 323 healthy adolescents reported a correlation of 0.42 (94) and a study among adults . There are also other reasons to why HOMA-IR and HOMA-B only correlate modestly with gold standard estimates. HOMA measures are derived from fasting samples of insulin and glucose and therefore estimates of insulin resistance and secretion is from the basal state. As a consequence the HOMA-IR and HOMA-B mainly describes hepatic insulin resistance and steady-state insulin secretion, whereas clamp estimates the stimulated extreme, which primarily reflects muscle insulin resistance (96). The use of the clamp is burdensome for participants and costly and therefore unsuited for an epidemiological study as the EYHS. Assuming that imprecision in estimation of insulin resistance and secretion is unrelated to the level of muscle strength and cardiorespiratory fitness, this will merely affect the precision of the estimate in the association analysis in study V and not the size of the estimate. We also attempted to estimate the association of muscle strength and cardiorespiratory fitness with the odds of insulin resistance in young adulthood. Since standards for insulin resistance in adolescents or adults have not been established based on HOMA-IR, we defined insulin resistance as being above the 75th percentile for HOMA-IR (97). Thus, the generalizability of these particular estimates derived in these analyses is uncertain.

Confounding

Observational studies are always prone to unknown confounding. Even careful collection of, and appropriately adjustment for known confounders cannot exclude the possibility of unknown confounding. In addition, variables identified as confounders can be imperfectly assessed and residual confounding could remain after statistical adjustment has been carried out. In study I, II, and VI where TV viewing and screen time use were exposures, a

number of other lifestyle factors may be either confounding or mediating the associations with the health outcomes. The descriptive statistics of the individual studies included in the meta-analysis in study I and study II indicate that TV viewing time is associated with a plethora of lifestyle factors, suggesting that both residual- and unknown confounding and mediation may be important to consider in association analyses and their interpretation. One major confounding or mediating factor is physical activity. TV viewing may displace time spent on other activity, most likely in the lower spectrum of the activity continuum, and this may explain the adverse effects observed. However, participants with excessive viewing time may also engage in less MVPA, although not as an effect of prolonged viewing time. In the ladder case activity serves as a confounding factor. Studies included in the meta-analysis (study I) and study II were each adjusted for MVPA. Although residual confounding may be still remain this suggest that the influence of prolonged TV viewing is not completely explained by lower MVPA. Self-reported MVPA is usually captured fairly accurate and precise. On the other hand, light activities such as standing, moving around slowly, and lifting objects during for example household tasks and social activities are more difficult to assess with sufficient precision and accuracy using questionnaires. Because engaging in one activity type is done at the expense of not engaging in another, excessive screen time use is likely to displace such activities and the associations we observe may therefore be explained by the lack of other activity in the spectrum below MVPA (<3 METs). Further studies are required to examine this. Prolonged TV viewing may also be associated with poor diet quality and higher quantity by encouraging excessive eating (98). Such associations may also be present beyond through the effect of viewing time and dietary factors may be both mediating and confounding the association of viewing time with T2D and CVDs risk. In the meta-analysis pooling results that were additional adjusted for BMI or another adiposity measure did not completely attenuate associations of viewing time with disease- or mortality outcomes. Furthermore, our studies on screen time use based on EYHS, associations to health outcomes persisted after additional adjustment for BMI or waist circumference. These additional analyses suggest that the association of viewing time with T2D and CVD risk were not solely mediated through greater adiposity. In addition, they also strengthen the confidence that other unmeasured- or imperfectly captured factors that are associated with lower or greater adiposity are not completely explaining these associations. However, although we have tried our best to limit the possibility of confounding, we still cannot exclude the possibility that residual- and unknown

confounding is a plausible explanation to these results and further randomized efficacy trials on this topic are needed to confirm this.

In the analyses of weight training with T2D risk in study III a comprehensive characterization of study participants on many important determinants of T2D were assessed either biannually or every four years. Using these data we were able to extensively control for major confounding factors during the entire 18-year follow-up period. Yet residual confounding in particular from other physical activities could be of concern considering that men who engage in weight training are likely to engage in other physical activities as well. To further rule out this possibility we restricted the analyses to individuals reporting no other activity, and the results of this analyses strengthened our confidence that this was not the case.

Reverse causation bias

If the estimate of association can be partly or completely attributable to the effect of the outcome on the exposure reverse causation bias or bidirectional association are present. In the studies on TV viewing and screen time viewing the increase in risk of T2D, CVDs, and mortality could also be attributable to presence of disease or subclinical disease at some participants at baseline and this could have an effect on TV viewing time (e.g. increases use). If that is the case the association of viewing time and disease or mortality risk may be overestimated. Thus, a prospective study that carefully has assured that the direction of association (i.e. that the exposure occurred before the outcome) may still be vulnerable to reverse causation bias or bidirectional association. Studies included in the meta-analysis carefully excluded diseased participants at baseline, and several of the studies performed sensitivity analysis excluding cases occurring during the first one or two years of follow-up which did not indicate possibility of reverse causation bias. In study II all participants were healthy adolescents at baseline, however, a prospective association of screen time use with CVD risk factors may also be a result of reverse causation bias. It may be that participants being overweight or obese or at the projection to become overweight at baseline as a result would increase their viewing time by discouraging active behaviors. As previous prospective studies among children and youth have indicated that adiposity may predict sedentary time (67), we also analyzed whether BMI or WC in adolescence was associated with screen-viewing time in young adulthood. These analyses did not suggest that adiposity predicted viewing time. Furthermore,

adjustment for adiposity in the association of viewing time with composite CVD risk factor score (not including adiposity) had only minor impact. Collectively, these analyses revealed no evidence of reverse causation bias.

In study III we limited the possibility of reverse causation bias by excluding participants with chronic disease at baseline, and in addition we further evaluated the possibility by comparing estimates of association in the primary Cox model (e.g. cumulative exposure status on weight training in 1990-1996 was used to predict T2D risk from 1996 to 1998) with an analysis using a 4-year lag in exposure classification (e.g. exposure status on weight training in 1996 was used to evaluate risk of T2D from 1998 to 2000). This comparison revealed no indication of reverse causation bias.

As study IV and V were prospective it enhanced our ability to explore the temporal relation between isometric muscle strength and CVD risk factors and indices of glucose metabolism. Yet, as isometric muscle strength was only assessed at baseline we had no possibility of evaluating the possibility of the direction of association being opposite. However, we would presume the existence of such relation would stem from individuals being overweight or obese and as a result discourage active behaviors, which in turn could lower their trunk muscle strength. However, as we found that the associations were robust to adjustment for various confounding factors including BMI or waist circumference, this limits the possibility of reverse causality. The inverse associations of screen time use and muscle strength observed in study VI could also be a result of reverse-causality, particularly as the study was cross-sectional. Thus, we cannot exclude that screen time use could increase as a result of poor strength.

Generalizability

Population characteristics in individual studies in the pooled analyses in study I were diverse. Studies were based on European-, Australian and US populations of men and women, and consistent results with a low or moderate heterogeneity in estimates of associations was observed. Together this strengthens the generalizability of the pooled estimates of association. The studies based on EYHS were from a random sample of Danish youth residing in the municipality of Odense, the third largest city of Denmark, with initial participation rate of around 60%. Although drop out and missing data during follow-up was substantial, our sensitivity analysis did not indicate selection bias and this gives us confidence that the results we have obtained have external validity to the source

population. However, larger samples from other countries are needed to further evaluate the generalizability of our findings in these studies. The generalizability of our results of study III may be limited because the cohort consist of men only, is largely white, and homogenous with respect to occupation (health professionals). Thus, the conclusions from this study may not be generalizable to women and other ethnic groups.

Main findings in relation to other studies

The meta-analysis of prospective studies examining associations of TV viewing time with the risk of T2D, CVDs, and mortality of all causes are supported by other meta-analyses and systematic reviews published recently. Wilmot et al. (99) meta-analyzed published cross-sectional and prospective studies until January 2012 reporting on the association of sedentary time, regardless of type, with the risk of T2D, CVDs, and mortality from all causes. This analysis similarly found that sedentary time was consistently associated with greater risk of these health outcomes. In a recent study, Ford et al. (100) meta-analyzed all prospective cohort studies examining the association between screen time and fatal and non-fatal CVD with inclusion of two new additional studies (101, 102) not included in study I of this thesis. This analysis also found that prolonged viewing time was associated with greater risk of fatal or non-fatal CVDs (RR=1.17 [95%CI 1.13-1.20]) per 2 hours/day). A number of prospective studies have also reported on the association of total sedentary behavior and mortality risk from CVDs and all causes (101, 103-108). These studies have mostly reported that excessive time spent sitting increases the risk of premature mortality independent of MVPA. The two largest studies conducted (in total including more than 400.000 individuals) also reported that high amounts of MVPA are unable to fully mitigate mortality risk associated with excessive daily sitting time (101, 107). Only one study has been published using accelerometer to assess sedentary time. This recently published study, based on the National Health and Nutrition Examination Survey (NHANES) data, reported that excessive sedentary time among 1906 individuals was associated with greater risk of morality from all-causes independent of MVPA, however, the participants were only followed for an average of 2.8 years and only 145 deaths occurred (108). Further studies using objectively measured total sedentary time with greater size and longer follow-up are therefore required.

Our subsequent analyses of youth from EYHS followed into young adulthood supports the findings from the meta-analysis conducted in study I and suggest that efforts to reduce both TV viewing time and computer use earlier in life may be valuable

for primordial prevention of CVD risk. This is also supported by a study conducted among New Zealanders followed from childhood to young adulthood (41). In this study Hancox et al. reported that prolonged TV viewing in childhood and adolescence was associated with greater BMI, lower cardiorespiratory fitness, and raised cholesterol in young adulthood independent of physical activity level and other confounding factors. The few number of randomized controlled trials on the effect of TV viewing time restriction on health outcomes that has been carried out to date generally supports the results from the prospective observational studies. A randomized school-based study of 192 9-year old children found that reducing TV viewing and video game time for 6-months slowed the increase in BMI and decreased the number of meals eaten in front of the TV but it did not have an effect on change in self-reported PA (109). Another study of 70 children with BMI above the 75th percentile showed that reducing TV- and computer time by 50% over two years produced a significant reduction of zBMI and energy intake but no effect was observed for objectively measured PA (110). A short term randomized study in 36 overweight or obese adults did not find a significantly greater change in energy intake or BMI after restricting TV viewing time by 50% in a period of three weeks, but a significant increase in objectively measured energy expenditure was observed (33). These experimental studies suggest that reducing TV viewing can lead to improvement in diet, physical activity, or BMI but further large scale efficacy studies are needed to confirm this with more confidence.

We are only aware of one other study examining the association of screen time viewing and trunk muscle strength described in study VI. Comparable results were obtained in a cross sectional study among Finnish young adults (111). An inverse association of TV viewing with isometric trunk muscle strength assessed using similar procedures were reported being independent of self-reported “brisk” physical activity and smoking status, but they did no adjust their analyses for cardiorespiratory fitness and other lifestyle- and socio-demographic factors. The study did not analyze computer use and did not adjust the analysis for adiposity that could further indicate confounding by other unmeasured factors associated with young adult lifestyle. Our study is also in agreement with a prospective study of Canadian toddlers followed until 2nd grade (112). In that study increases in parental reported TV viewing time between the age of 2.5 and 4.5 years predicted shorter long jump performance at 8 years of age independent of parental reported physical activity, other child and family characteristics including weight status at follow-up. Furthermore, two cross-sectional studies carried out in the 1970’ies

and early 1980'ies have reported inverse associations of TV viewing time with components of muscle strength and fitness (113, 114). We know of no experimental studies examining the effect of reducing any type of sedentary behavior including screen-based behaviors on muscle strength.

The association of weight training with T2D risk (study III) is, to the best of our knowledge, the first study examining this. Furthermore, the studies IV and V are the first to report associations of muscle strength in youth with CVD risk factors and indices of glucose metabolism in adulthood independent of cardiorespiratory fitness. The results of study III, IV, and V are supported by a number of observational and experimental addressing analogous study questions. A study conducted among 1,543 adults from the Canadian Physical Activity Longitudinal Study (51) found that a number of indicators of muscular fitness (e.g. grip strength and push-ups) were inversely associated with the risk of T2D, however, it was not reported whether these associations were independent of cardiorespiratory fitness and other major determinants of T2D risk beyond age, sex, smoking status and alcohol consumption (51). Two studies based on cross-sectional NHANES data have reported that muscle mass (115) and engagement in muscle strengthening activities (116) are inversely associated with insulin resistance. A previous study among children followed into adolescence has shown that improvement in handgrip strength during follow-up was associated with favorable changes in BP, lipid levels, and adiposity independent of cardiorespiratory fitness (117). Three population-based cross-sectional studies among children and adolescents have reported that muscle strength or muscular fitness were associated with clustered metabolic risk or insulin resistance independent of cardiorespiratory fitness (56, 57, 118). Three randomized controlled trials have been carried out among youth comparing the effect of resistance training on insulin resistance or glycemic control with a pure control group. A small scale trial among n=22 overweight Latino adolescent males found that 16 weeks of resistance training performed twice a week markedly increased insulin sensitivity (119). Another randomized trial among n=78 overweight or obese children and adolescents from New Zealand reported that the effect of 8 weeks of resistance training performed twice a week had no significant effect on insulin resistance, however, results were in the expected direction and the training improved abdominal and general adiposity (120). A recent efficacy trial among n=45 obese adolescents boys reported that both aerobic exercise and resistance training for 3 months were effective for reducing adiposity but only the resistance exercise group improved insulin sensitivity (121). Several trials evaluating the

effect of resistance exercise or the combination of resistance exercise and aerobic exercise on glycemic control have been completed among adults with T2D (43-48) and the collective evidence supports that resistance exercise is beneficial for improving glycemic control among individuals with T2D (21). Furthermore, the results from these and other randomized trials among healthy adults also support that resistance exercise alone can improve blood pressure, lipid levels and reduce adiposity (122). The overall pool of observational- and experimental studies generally supports our findings in study III, IV, and V. Though, in a secondary analysis in study III we found that no association of weight training with mortality risk of all-causes or from CVDs. It is unlikely that the lack of association was due to lack of statistical power as we had a substantial number of deaths from all-causes and CVDs in our analyses. In a previous study based on the Canadian Fitness Survey, several measures of muscular strength and endurance were examined in relation to mortality risk (54). Of these only greater abdominal muscular endurance was associated with lower mortality risk. In a report from the Aerobic Centre Longitudinal Study low muscle strength was reported being associated with higher risk of premature mortality independent of cardiorespiratory fitness and other confounders in men (50). However, they reported no association with mortality from CVD in multivariable adjusted analyses. Based on these and our analyses among men from HPFS, this suggest that aerobic exercise should not be replaced by muscle strengthening activities, but rather supplemented.

Biological mechanisms

T2D and CVDs develop slowly over many years and their exact molecular etiology are therefore difficult to study. As a consequence these remain poorly understood. Though, factors such as obesity, insulin resistance, high BP, and raised levels of triglycerides are well-established intermediate disease traits that can be studied more easily. The biological mechanisms underlying the associations described in the studies I-VI can only to a small extent be addressed by our own data. In study I and II we attempted to meta-analyze all studies with and without adjustment for an adiposity measure to examine the extent to which the associations of TV viewing with risk of T2D, CVDs, and all-cause mortality were explained by the influence of TV viewing on adiposity. These analyses support that adiposity explained some of these associations, in particular for T2D. This is also supported by experimental studies conducted in children described previously (109, 110). The energy expenditure component of the adverse effect of TV viewing time could

stem from displacing time spent on lighter intensity activities. A previous experimental study suggest that these types of activities can contribute substantially to higher energy expenditure beyond the resting metabolic rate (123). Furthermore, a study comparing habitual posture allocation during 10 days between obese and lean "couch potato" individuals found that obese individuals on average were seated for 164 min more every day (124). Recently, two short-term (1 day) trials have been conducted evaluating the effect of sitting time on glucose metabolism outcomes. Stephens et al. (125) compared 1 day of no sitting with 1 day of prolonged sitting among non-obese healthy adults using a cross-over design. Whole body insulin resistance was increased after 1 day of prolonged sitting compared with no sitting and matching energy intake to the lower energy expenditure requirement in the day with prolonged sitting did not prevent the increase in whole body insulin resistance. Using a cross-over design Dunstan et al. (126) compared the acute effect of breaking up prolonged sitting by 2-min short bouts of activity (treadmill) of either light or moderate intensity every 20 min during 5 hours among overweight or obese adults. Relative to prolonged sitting, the postprandial glucose and insulin responses were reduced after both activity-break conditions (light or moderate). These two short-term trials suggest that the adverse acute effect of prolonged sitting on glucose metabolism may be prevented by lighter intensity activity such as slow walking and could explain some of the biological mechanisms of the sedentary component of TV viewing time. If generalized to long-term this suggest that promoting light activity (or limiting prolonged sitting) may be beneficial for preventing T2D and CVDs at least through improving insulin sensitivity. Still, further studies are required to clarify the mechanisms behind the adverse effects of prolonged TV viewing and sedentary time.

As described previously, many randomized trials have examined the effect of resistance exercise on outcomes such as obesity and insulin resistance in secondary or tertiary prevention studies. These trials help explain the biological mechanism behind the associations we observe in studies III-V. However, many physiological studies have addressed mechanisms on the molecular level by which resistance exercise improves traits such as insulin sensitivity. This topic has been extensively reviewed in the literature (127-129). Resistance exercise may decrease the risk of T2D through several mechanisms. Because aging is associated with increasing loss of lean body mass, one important role may be the effect of resistance exercise on skeletal muscle mass maintenance (129). However, there are possibly also effects of this exercise type beyond muscle mass growth or maintenance. Other effects reported for resistance exercise

include increases in glycolytic capacity and up regulation of proteins in the insulin-signaling cascade (130). These local adaptations increase insulin action and enhance the capacity of glucose utilization. A reduced glucose stress resulting from an increase in insulin sensitivity of skeletal muscle may improve the secretory capacity of the beta-cells and explain the associations of muscle strength in youth with beta-cell function in young adulthood in study V.

Although we are unaware experimental studies examining the effect of reducing any type of sedentary behavior on muscle strength, one previous randomized trial may help to explain some of the association we observe between screen time use and isometric trunk muscle strength described in study VI. A small scale randomized trial have examined the effect of changing school furniture to adjustable desks and chairs with sitting trunk–thigh angle adjusted to 135° compared with traditional school desks and chairs with sitting trunk–thigh angle of 90° for a period of 2 years among high school student. They reported that the intervention increased isometric abdominal- and back muscle strength (131). These results support that particular postures while sitting are important for development or maintaining of trunk muscle strength. But additional studies are needed to conclude that excessive screen time use can cause lower muscle strength and disentangle whether this stems from the nature of the posture (seated/lying) and/or from the fewer posture allocations.

Conclusions

The overall conclusions of this thesis are that reducing prolonged screen time viewing and engagement in muscle strengthening activities or maintaining high muscle strength in adults and youths respectively could be important actions in preventive measures against T2D and CVD. Thus, in addition to engagement in aerobic MVPA and maintaining and improving cardiorespiratory fitness, efforts to shift the population distribution of muscle strength and screen time viewing upwards (to the right) and downwards respectively, may be valuable for prevention of these diseases and raised levels of their biological risk factors such as insulin resistance and adiposity. The conclusions based on the six studies are described below:

Quantitatively using all available prospective studies, prolonged TV viewing time was consistently associated with greater risk of T2D, fatal or non-fatal CVD and mortality from all-causes in a dose-response manner. The results of the meta-analysis provide evidence that each 2 hours/day difference in TV viewing time increase the risk of T2D and CVD by 20% and 15% respectively. The risk of all-cause mortality appeared to increase with TV viewing time above 3 hours/day. However, more studies are needed to quantify the nature of the relationship between TV viewing and these health outcomes with greater confidence and preclude that publication bias could influence the results.

Prolonged TV- and total screen time viewing during leisure time in adolescence, and increases in these behaviors, were associated with unfavorable levels of several risk factors for CVDs in young adulthood. Dose-dependent relationships were observed and associations persisted with adjustment for major determinants of CVD risk including adiposity. The findings provide support for recommending limiting prolonged screen time viewing among youth as recently suggested by several organizations and authorities.

Engagement in weight training was associated with a reduced risk of T2D in a dose response manner independent of aerobic physical activity. The magnitude of risk reduction associated with weight training was close to that of aerobic activity and support that weight training is a valuable alternative for individuals having difficulty adhering to aerobic activity. In addition, results indicated that adding weight training to aerobic activity, consistent with the current recommendations may give further protection from

T2D. No associations were observed between weight training and risk of mortality from CVD or all-causes. Overall, this study suggests that aerobic exercise should not be substituted for muscle strengthening activities, but rather supplemented among men.

Greater isometric muscle strength of the abdomen and back in youth was associated with lower levels of CVD risk factors in young adulthood. Dose-response relationships were generally observed for these associations even after adjustment for cardiorespiratory fitness, other potential confounding factors and adiposity. These results support a specific emphasis on participation in muscle strengthening activities for primordial prevention of CVD risk in accordance to the current guidelines for physical activity in youth.

Low isometric muscle strength and cardiorespiratory fitness in youth were each independently associated with adverse levels of fasting insulin, insulin sensitivity, and beta-cell function in young adulthood. The magnitude of associations for isometric muscle strength and cardiorespiratory fitness were very similar, which suggest that participation in muscle strengthening activities may be equally important as participating in aerobic activities in youth for maintaining healthy insulin sensitivity and beta-cell function later in life. Furthermore, associations for isometric muscle strength and cardiorespiratory fitness with these outcomes appeared additive, which indicate that it may be beneficial to increase muscle strength at any level of cardiorespiratory fitness.

In a cross-sectional analysis excessive screen time use in youth was inversely associated with isometric trunk muscle strength independent of cardiorespiratory fitness, lifestyle behaviors, adiposity, and socio-demographic factors. We were unable to determine whether this association was explained by the prolonged time spent in a seated or lying position and the possible fewer posture allocations or if other factors related to screen time use explains the result. Further observational- and experimental studies are needed to examine this in detail.

Perspectives

In the studies included in the present thesis we have addressed the possible health consequences of prolonged TV-viewing and screen time use and the health benefits of engagement in muscle strengthening activities and high muscle strength in relation to T2D, CVD, and their biological risk factors. Using mostly prospective collected observational data we have analytically attempted to overcome and address possible bias inherent to these types of studies. Nevertheless, limitations to the studies are still a concern and in the following paragraphs, suggestions are given to future research to further explore the health impact of these exposures and overcome the limitations to current studies, including the studies that this thesis is based on.

Further observational studies on the associations of total sedentary time with morbidity and mortality that adjust the analysis for TV viewing time (in addition to all other major confounders) are required to give an answer to what extent TV viewing time is driving the association of total sedentary time with health outcomes. The results from such analyses would be important for guiding prevention strategies. As mentioned previously, the two largest studies conducted reported that high amounts of MVPA are unable to fully mitigate mortality risk associated with excessive daily sitting time (101, 107). It would be expected that the increase in risk would be diminished at some amount of MVPA and further describing this in detail would be important as many individuals have numerous sedentary hours during a day. Previous estimates of populations-attributable fraction suggest that excessive total sitting time is responsible for 7%-27% of all deaths independent of MVPA (107, 132). If these estimates are unbiased a major public health benefit could be gained by reducing total sitting time beyond having populations increasing their MVPA. Thus, observational studies using unbiased objectively measured total sedentary behavior and other intensity components of PA are required to overcome possible differential- and non-differential measurement error associated with self-reported sedentary behavior and physical activity. Currently the use of accelerometry in the assessment of sedentary time has not been rigorously evaluated with respect to impact of data reduction choices and participants adherence to monitoring protocol on error in estimation of time spent being sedentary. This type of work is essential for further expanding the use of accelerometers in observational studies of sedentary behavior. Finally, additional corroborative evidence from randomized controlled efficacy trials in populations of children, youth, and adults will strengthen the

inference that TV viewing and total sedentary time is causally related to the development of T2D and CVDs. Until then it may be premature to include total sedentary time to the group of independent risk factors for T2D and CVDs.

Among children and youth the evidence from both randomized controlled trials and well conducted prospective observational studies suggesting that prolonged TV viewing time has a detrimental effect on adiposity, in particular, is accumulating. A continuously updated detailed systematic evaluation of the available evidence, including an analysis of both harms and benefits, is important to carry out to justify- and further give detail and quality to the current (and perhaps coming) recommendations on limiting viewing time. The health consequences of the use of new media devices such as tablets have not been reported in any type of study. Today iPads is introduced already in toddler care and kindergartens and widely used by small children in many homes, and the potential negative and positive impacts of this particular media device are crucial to explore in future studies.

In our studies of muscle strength as exposures we used isometric abdominal- and back muscle strength. Although previous studies have reported moderate to strong correlation between isometric- and dynamic muscle strength (133), additional larger scale studies are warranted using similar- or alternative methods including different muscle groups and types of strength measures to study associations to CVD risk factors and glucose metabolism outcomes. As the particular isometric assessments we performed in our studies were easily carried out, fast, do not require expensive equipment, and previous studies have proven high reliability, their predictive validity for disease endpoints and mortality should also be examined.

Our study of weight training and T2D risk was restricted to men. It remains uncertain whether engagement in resistance exercise is associated with reduced T2D risk in women. In addition, lower intensity muscular strength- and conditioning exercises such as pilates and yoga are popular physical activities among women. These types of activities may also be valuable for increasing and maintaining muscle strength and endurance (134, 135), however, their role in T2D and CVD prevention is also relatively unknown. Thus, further observational studies are needed to examine this, and detailed examination of the influence of duration, type, and intensity of muscle strengthening activities on the risk of these health outcomes are warranted. Finally, studies examining the associations of muscle strengthening activities with the risk of other outcomes, including coronary heart disease, stroke, total- and cause-specific mortality are needed.

The main limitations of our observational studies are that we cannot exclude the possibility of bias such as confounding and reverse causation bias. Pursuing randomized controlled efficacy trials will be an important next step to infer causality. Such trials are feasible for both limiting screen time viewing or total sedentary time and engagement in muscle strengthening activities. While identification of causal risk factors is the outset for prevention, it is clearly not sufficient for curbing the future burden of disease. Ideally, when risk factors have been identified various effectiveness studies (pragmatic trials) should be carried out in populations to give answers to what kind of preventive measures, including types of policies and programs, that are effective for changing activity patterns and subsequently for preventing T2D, CVDs, and premature mortality. Furthermore, cost-effectiveness evidence from such effectiveness trials that show that the interventions studied can be scaled up is equally important. These types of studies are essential for achieving quality in the development of public health strategies.

English summary

Background

Lack of aerobic type physical activity and low cardiorespiratory fitness are well-established risk factors for type 2 diabetes (T2D) and cardiovascular diseases (CVDs). In contrast, more limited evidence from prospective studies exists on the possible risk of engagement in types of activities that are considered being sedentary such as TV viewing and other screen time use behaviors, and on the benefits of muscle strengthening type activities or muscle strength in relation to prevention of these diseases.

Aims and methods

The aim of this thesis was to investigate the associations of screen time use with the risk of T2D, CVDs, and premature mortality in adults and with their biological risk factors in youth followed into young adulthood. In addition, we aimed to examine the association of weight training with the risk of T2D among men and the association of muscle strength with CVD risk factors and indices of glucose metabolism in youth followed in to young adulthood. Finally, we aimed to examine the association of screen time use with trunk muscle strength in youth. To address these aims we used data from observational studies conducted among youth and adults. We used data from published prospective studies identified in a systematic literature search, to quantify an overall estimate of associations of TV viewing with T2D, CVDs, and premature mortality via meta-analyses. We used data from the Danish part of the ongoing prospective cohort study the European Youth Heart Study of youth followed in to young adulthood with up to 12-years of follow-up. In 1997/98 or 2003/04 EYHS participants completed a clinical examination including a fasting blood sample, anthropometry, blood pressure, cardiorespiratory fitness, isometric trunk muscle strength, and participants and their parents reported a number of lifestyle habits and socio-demographic factors respectively in a questionnaire. In 2009/10 these participants, now being young adults, were followed up using fairly similar assessment procedures. Furthermore, we used data from the Health Professionals Follow-up Study (HPFS), which is an ongoing prospective cohort study of 32,002 US male health professionals that were free of diabetes, cancer, and cardiovascular diseases at baseline in 1990 and followed during 18 years with biannual assessment of various lifestyle exposures and disease outcomes including self-reported information on aerobic physical activity, weight training, and other lifestyle factors.

Results

The meta-analysis suggested that prolonged TV viewing time was consistently associated with greater risk of T2D, fatal or non-fatal CVD, and mortality from all-causes. The results indicted dose-dependent associations; each 2 hours/day difference in TV viewing time increased the risk of T2D, CVD, and all-cause mortality by 20%, 15%, and 13% respectively. In the European Youth Heart Study, prolonged TV- and total screen time viewing during leisure time in adolescence, and increases in these behaviors, were associated with unfavorable levels of several risk factors for CVDs in young adulthood. Dose-dependent relationships were observed and associations persisted with adjustment for major determinants of CVD risk including adiposity. Including change in TV viewing and computer use in the same multivariable adjusted model, changes in both types of screen use were independently associated with BMI and plasma insulin.

In the HPFS, engagement in weight training was associated with a reduced risk of T2D in a dose response manner independent of aerobic physical activity. The magnitude of risk reduction associated with weight training was close to that of aerobic exercise. Engaging in weight training or aerobic exercise of at least 150 min/week was independently associated with a lower risk of T2D of 34% and 52% respectively. In addition, results indicated that adding weight training to aerobic activity, consistent with the current recommendations give further benefit for reducing T2D risk. Weight training was not associated with mortality from CVD or all causes. In the European Youth Heart Study low isometric muscle strength of the abdomen and back in youth was associated with adverse levels of a number of CVD risk factors, insulin resistance, and beta-cell function in young adulthood independent of cardiorespiratory fitness, other lifestyle, and socio-demographic factors. Dose-response relationships were generally observed for these associations even after adjustment adiposity. Finally, excessive screen time use in youth from the European Youth Heart Study was inversely associated with isometric trunk muscle strength independent of cardiorespiratory fitness, lifestyle behaviors, adiposity, and socio-demographic factors.

Conclusions

In prospective studies of diverse populations prolonged TV viewing time was consistently associated with greater risk of T2D, fatal or non-fatal CVD and mortality from all-causes, consistent with a dose-response relationship. Furthermore, prolonged TV- and total

screen time viewing during leisure time in youth, and increases in these behaviors into young adulthood, were associated with unfavorable levels of several risk factors for CVDs in young adulthood. We also found that engagement in weight training was associated with a reduced risk of T2D among men independent of aerobic physical activity. Since we found no association of weight training with mortality from CVDs or all-causes in multivariable adjusted analyses this study suggests that aerobic exercise should not be substituted for muscle strengthening activities, but rather supplemented among men for overall prevention of these health outcomes. These results were generally supported by our prospective studies among youth followed into adulthood. Low isometric muscle strength and cardiorespiratory fitness in youth were each independently associated with adverse levels of fasting insulin, insulin sensitivity, and beta-cell function in young adulthood. Furthermore, combined associations indicate that it may be beneficial to increase muscle strength at any level of cardiorespiratory fitness. We also found that low isometric muscle strength of the abdomen and back in youth were associated with adverse levels of several CVD risk factors in young adulthood. Finally, a cross-sectional analysis revealed that excessive screen time use was inversely associated with isometric trunk muscle strength and suggest that reducing screen time habits also may be important for maintaining trunk muscle strength besides from influencing cardiorespiratory fitness.

Collectively, the results of the thesis support that reducing screen time use and engagement in muscle strengthening activities or maintaining high muscle strength in adults and youths respectively could be important actions in preventive measures against T2D and CVDs and raised levels of their biological risk factors.

Danish summary

Baggrund

Betydningen af aerob fysisk aktivitet og kardiorespiratorisk kondition i forhold til forebyggelse af type 2 diabetes (T2D) og hjertekarsygdomme er veldokumenteret. Derimod er det mere uklart hvilken rolle stillesiddende aktiviteter og muskelstyrke prægede aktiviteter spiller i forhold til forebyggelse af disse sygdomme.

Formål og metoder

Formålet med denne afhandling var at undersøge om et højt forbrug af TV og skærmtid er forbundet med øget risiko for T2D og hjertekarsygdomme blandt voksne, samt om de er forbundne med biologiske risikofaktorer for disse sygdomme blandt unge fulgt ind i voksenalderen. Desuden var formålet at undersøge om styrketræning er forbundet med nedsat risiko for udvikling af T2D, samt at undersøge om muskelstyrke er associeret til insulin resistens, beta-celle funktion og biologiske risikofaktorer for hjertekarsygdomme blandt unge fulgt ind i voksenalderen. Endelig var formålet at undersøge associationen mellem forbruget af skærmtid og muskelstyrke blandt unge. Til at besvare disse formål benyttedes data fra observationsundersøgelser gennemført blandt unge og voksne. Data fra publicerede prospektive kohorteundersøgelser var identificeret via en systematisk søgning og brugt til at kvantificere associationen mellem TV forbrug og risiko for T2D, hjertekarsygdomme og død af alle årsager i en meta-analyse. Derudover benyttede vi data fra the European Youth Heart Study (EYHS), som bygger på en tilfældig stikprøve af danske unge fulgt i op til 12 år ind i voksenalderen I 1997/98 eller i 2003/04 gennemførte 14-16-årige EYHS deltagere en klinisk undersøgelse som inkluderede en fastende blodprøve, antropometri, blodtryksmåling, kardiorespiratorisk kondition, isometrisk muskelstyrke af bug og ryg, og deltagerene og deres forældre besvarede spørgeskema angående livsstil, personlige, og socio-demografiske faktorer. I 2009/10 blev deltagerne fulgt op som unge voksne og de fleste tilsvarende målinger blev fortaget i denne målerunde. Vi benyttede også data fra et amerikansk prospektivt kohortestudie (the Health Professionals Follow-up Study (HPFS)). I dette studie fulgtes 32,002 amerikanske sundhedsprofessionelle mænd der ikke havde cancer, diabetes, eller hjertekarsygdomme ved baseline i 1990 gennem 18 år. Gennem hele opfølgningsperioden udfyldte deltagerne, hvert andet eller fjerde år, spørgeskema

angående bl.a. forskellige livsstilsmønstre og sygdoms-opståen inklusiv information om aerobe aktiviteter og styrketræning.

Resultater

Resultaterne fra meta-analysen viste at et højt TV forbrug var forbundet med øget risiko for T2D, dødelig- og ikke dødelig hjertekarsygdom og for tidlig død. Der blev fundet dosis-respons sammenhænge; for hver to timers forskel i TV forbrug øgedes risikoen for T2D, hjertekarsygdom of død af alle årsager med henholdsvis 20%, 15% og 13%. I EYHS fandt vi at et højt forbrug af TV og total skærm tid i ungdommen var forbundet med forhøjede niveauer af flere risikofaktorer for hjertekarsygdomme. Ligeledes fandt vi, at en stigning i disse adfærdsmønstre fra ung til voksen var associeret med ugunstige niveauer af flere risikofaktorer for hjertekarsygdomme i ung voksenalder. Der sås dosis-respons sammenhænge og associationen til en samlet hjertekarsygdomsrisikofaktor score var uafhængigt af fedme. Desuden var ændringer i både TV og computerforbrug uafhængigt af hinanden, positivt associeret til koncentrationen af plasma insulin og BMI i voksenalderen.

Styrketræning var forbundet med nedsat risiko for T2D blandt amerikanske mænd fra HPFS. Sammenhængen var uafhængig af aerob fysisk aktivitet og andre konfoundere og risikoreduktionen var dosis-respons afhængig. Deltagelse i styrketræning og aerob fysisk aktivitet i minimum 150 min/uge var associeret med henholdsvis 34% og 52% lavere risiko for T2D uafhængigt af hinanden. Der sås ingen association mellem styrketræning og død af hjertekarsygdomme eller af alle årsager i multivariable analyser. Mænd der rapporterede at de både deltog i styrketræning og aerobe aktiviteter havde den største reduktion i risiko for T2D. I EYHS fandt vi at lav isometrisk bug- og ryg styrke som ung var forbundet med ugunstige niveauer af insulin resistens, beta-celle funktion og risikofaktorer for hjertekarsygdomme såsom BMI, blodtryk og triglycerid uafhængigt af kardiorespiratorisk kondition og andre konfoundere. Der sås dosis-respons sammenhænge - også efter yderligere justering for BMI eller taljeomkreds. Det sidste studie baseret på tværsnitsmateriale af unge fra EYHS, viste at forbruget af skærmtid var invers associeret med isometrisk bug- og rygstyrke uafhængigt af kardiorespiratorisk kondition, BMI (eller taljeomkreds) og andre konfoundere.

Konklusion

Den kummulative evidens fra prospektive kohortestudier gennemført i populationer i forskellige verdensdele indikerer en dosis-respons sammenhæng mellem TV forbrug og risiko for T2D, dødelig- og ikke dødelig hjertekarsygdom og for tidlig død. Disse fund støttes af vores prospektive studie af unge, hvor et højt forbrug af TV og total skærm tid i ungdommen, og en stigning i forbruget i disse adfærdsmønstre fra ung til voksen var associeret med ugunstige niveauer af flere risikofaktorer for hjertekarsygdomme i ung voksenalder. Vi fandt også at styrketræning blandt mænd var forbundet med lavere risiko for T2D uafhængigt af aerob fysisk aktivitet. Derimod fandt vi ingen association til død af hjertekarsygdomme eller af alle årsager, hvilket tilsammen indikerer at styrketræning bør være et supplement til aerob fysisk aktivitet snarere end et alternativ. I vores prospektive studier af unge fandt vi negative dosis-respons sammenhænge mellem isometrisk bug- og ryg styrke i ungdommen og insulin resistens, beta-celle funktion og flere risikofaktorer for hjertekarsygdomme i ung voksenalder. Endelig viste et tværsnitsstudie af unge at forbruget af skærmtid var invers associeret med isometrisk bug- og rygstyrke, hvilket indikerer at reduktion i forbruget af skærm tid blandt unge er vigtigt for opretholdelse af bug- og ryg styrke foruden at være betydningsfuldt for kardiorespiratorisk kondition.

Tilsammen antyder resultaterne fra denne afhandling at en reduktion i forbruget af tid foran skærmen og deltagelse i muskelstyrkeprægede aktiviteter eller opretholdelse af muskelstyrke blandt voksne og unge er vigtige strategier til forebyggelse af T2D, hjertekarsygdomme og deres biologiske risikofaktorer.

References

1. World Health Orgianization. NCD mortality and morbidity. Global Health Observatory (GHO). 2011.
2. International Diabetes Federation. IDF DiabetesAtlas. Epidemiology and Mobidity. In: International Diabetes Federation. Available from http://www.idf.org/. Accessed on 15 Nov 2012.
3. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5·4 million participants. The Lancet. 2011;377(9765):568-77.
4. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3·0 million participants. The Lancet. 2011;377(9765):578-86.
5. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. The Lancet. 2011;378(9785):31-40.
6. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ, et al. National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. The Lancet. 2011;377(9765):557-67.
7. Shaw JE, Sicree RA, Zimmet PZ**.** Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice. 2010;87(1):4-14.
8. Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K**.** The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia. 2008;51(12):2187-96.
9. Chen L, Magliano DJ, Zimmet PZ**.** The worldwide epidemiology of type 2 diabetes mellitus - present and future perspectives. Nat Rev Endocrinol. 2012;8(4):228-36.

10. Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005-2006. Diabetes Care. 2009;32(2):342-7.
11. Dansk Hjertestatistik 2010. Hjerteforeningen og Statens Institut for Folkesundhed ved Syddansk Universitet. 2011.
12. Sattelmair J, Pertman J, Ding EL, Kohl HW, Haskell W, Lee IM. Dose Response Between Physical Activity and Risk of Coronary Heart Disease / Clinical Perspective. Circulation. 2011;124(7):789-95.
13. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical Activity of Moderate Intensity and Risk of Type 2 Diabetes. Diabetes Care. 2007;30(3):744-52.
14. Kodama S SKTS, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. JAMA: The Journal of the American Medical Association. 2009;301(19):2024-35.
15. Zheng H, Orsini N, Amin J, Wolk A, Nguyen VT, Ehrlich F. Quantifying the dose-response of walking in reducing coronary heart disease risk: meta-analysis. Eur J Epidemiol. 2009;24(4):181-92. Epub 2009 Mar 22.
16. Sofi F, Capalbo A, Cesari F, Abbate R, Gensini GF. Physical activity during leisure time and primary prevention of coronary heart disease: an updated meta-analysis of cohort studies. Eur J Cardiovasc Prev Rehabil. 2008;15(3):247-57.
17. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. Eur J Cardiovasc Prev Rehabil. 2008;15(3):239-46.
18. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med. 2008;42(4):238-43.
19. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. The Lancet. 2012;380(9838):219-29.
20. Kodama S TSSK, et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: A meta-analysis. Archives of Internal Medicine. 2007;167(10):999-1008.

21. Umpierre D, Ribeiro PAB, Kramer CK, Leitao CB, Zucatti ATN, Azevedo MJ, et al. Physical Activity Advice Only or Structured Exercise Training and Association With HbA1c Levels in Type 2 Diabetes. JAMA: The Journal of the American Medical Association. 2011;305(17):1790-9.
22. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, et al. Effects of the Amount and Intensity of Exercise on Plasma Lipoproteins. New England Journal of Medicine. 2002;347(19):1483-92.
23. Davis Cl PNKWJL, et al. Exercise dose and diabetes risk in overweight and obese children: A randomized controlled trial. JAMA: The Journal of the American Medical Association. 2012;308(11):1103-12.
24. Physical Activity Guidelines Advisory Committee Report. Washington, DC: U.S.Department of Health and Human Services. 2008.
25. Department of Health UK. UK physical activity guidelines. 2011.
26. World Health Organization. Global Recommendations on Physical Activity for Health.
Geneva, Switzerland: WHO Press;. 2010.
27. TNS Gallup, Tv-meter årsrapport. Statistics Denmark. 2012.
28. Office for Official Publications of the European Communities. Time use at different stages of life. Results from 13 European countries. Luxembourg. 2003.
29. Australian Bureau of S. How Australians Use Their Time. Canberra, Australia: Commonwealth of Australia. 2008.
30. The Nielsen C. TV Usage Trends: Q3 and Q4 2010. New York, NY: State of the media. 2011.
31. Statistical Yearbook. Statistics Denmark. 2010.
32. Statistics Denmark (Danmarks Statistik. Statistiske Årbøger 2001-2011. København: 2001-2011) based on TNS Gallup and DR medieforskning.
33. Otten JJ, Jones KE, Littenberg B, Harvey-Berino J. Effects of Television Viewing Reduction on Energy Intake and Expenditure in Overweight and Obese Adults: A Randomized Controlled Trial. Archives of Internal Medicine. 2009;169(22):2109-15.
34. Editor's Correspondence: COMMENTS AND OPINIONS. Archives of Internal Medicine. 2010;170(13):1169-77.

35. Wiecha JL, Peterson KE, Ludwig DS, Kim J, Sobol A, Gortmaker SL. When Children Eat What They Watch: Impact of Television Viewing on Dietary Intake in Youth. Arch Pediatr Adolesc Med. 2006;160(4):436-42.
36. Wellman RJ, Sugarman DB, DiFranza JR, Winickoff JP. The Extent to Which Tobacco Marketing and Tobacco Use in Films Contribute to Children's Use of Tobacco: A Meta-analysis. Arch Pediatr Adolesc Med. 2006;160(12):1285-96.
37. Committee on Public Education. Children, Adolescents, and Television. Pediatrics. 2001;107(2):423-6.
38. Tremblay MS, LeBlanc AG, Janssen I, Kho ME, Hicks A, Murumets K, et al. Canadian Sedentary Behaviour Guidelines for Children and Youth. Applied Physiology, Nutrition, and Metabolism. 2011;36(1):59-64.
39. Australian Government, Department of Health and Ageing. Australia's Physical Activity Recommendations. Canberra, Australia: Department of Health and Ageing; 2004.
40. Tremblay M, LeBlanc A, Kho M, Saunders T, Larouche R, Colley R, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. International Journal of Behavioral Nutrition and Physical Activity. 2011;8(1):98.
41. Hancox RJ, Milne BJ, Poulton R. Association between child and adolescent television viewing and adult health: a longitudinal birth cohort study. The Lancet. 2004;364(9430):257-62.
42. Chinapaw MJM, Proper KI, Brug J, van Mechelen W, Singh AS. Relationship between young peoples' sedentary behaviour and biomedical health indicators: a systematic review of prospective studies. Obesity Reviews. 2011;12(7):e621-e32.
43. Sigal RJ, Kenny GP, BoulÇ NG, Wells GA, Prud'homme D, Fortier M, et al. Effects of Aerobic Training, Resistance Training, or Both on Glycemic Control in Type 2 Diabetes. Annals of Internal Medicine. 2007;147(6):357-69.
44. Church TS, Blair SN, Cocreham S, Johannsen N, Johnson W, Kramer K, et al. Effects of Aerobic and Resistance Training on Hemoglobin A1c Levels in Patients With Type 2 Diabetes. JAMA: The Journal of the American Medical Association. 2010;304(20):2253-62.
45. Dunstan DW, Daly RM, Owen N, Jolley D, de C, Shaw J, et al. High-Intensity Resistance Training Improves Glycemic Control in Older Patients With Type 2 Diabetes. Diabetes Care. 2002;25(10):1729-36.

46. Bacchi E, Negri C, Zanolin ME, Milanese C, Faccioli N, Trombetta M, et al. Metabolic Effects of Aerobic Training and Resistance Training in Type 2 Diabetic Subjects. Diabetes Care. 2012;35(4):676-82.
47. Balducci S ZSNA, et al. Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 diabetes mellitus: A randomized controlled trial: the italian diabetes and exercise study (ides). Archives of Internal Medicine. 2010;170(20):1794-803.
48. Castaneda C, Layne JE, Munoz-Orians L, Gordon PL, Walsmith J, Foldvari M, et al. A Randomized Controlled Trial of Resistance Exercise Training to Improve Glycemic Control in Older Adults With Type 2 Diabetes. Diabetes Care. 2002;25(12):2335-41.
49. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Rev. 2011(7):CD000333.
50. Ruiz JR, Sui X, Lobelo F, James R Morrow J, Jackson AW, Sjöström M, et al. Association between muscular strength and mortality in men: prospective cohort study. BMJ. 2008;337.
51. Katzmarzyk PT, Craig CL, Gauvin L. Adiposity, physical fitness and incident diabetes: the physical activity longitudinal study. Diabetologia. 2007;50(3):538-44.
52. Rantanen T, Harris T, Leveille SG, Visser M, Foley D, Masaki K, et al. Muscle Strength and Body Mass Index as Long-Term Predictors of Mortality in Initially Healthy Men. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2000;55(3):M168-M73.
53. Metter EJ, Talbot LA, Schrager M, Conwit R. Skeletal Muscle Strength as a Predictor of All-Cause Mortality in Healthy Men. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2002;57(10):B359-B65.
54. Katzmarzyk PT, Craig CL. Musculoskeletal fitness and risk of mortality. Med Sci Sports Exerc. 2002;34(5):740-4.
55. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, et al. Strength, But Not Muscle Mass, Is Associated With Mortality in the Health, Aging and Body Composition Study Cohort. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2006;61(1):72-7.

56. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc. 2009;41(7):1361-7.
57. Artero EG, Ruiz JR, Ortega FB, España-Romero V, Vicente-Rodríguez G, Molnar D, et al. Muscular and cardiorespiratory fitness are independently associated with metabolic risk in adolescents: the HELENA study. Pediatric Diabetes. 2011;12(8):704-12.
58. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of Observational Studies in Epidemiology. JAMA: The Journal of the American Medical Association. 2000;283(15):2008-12.
59. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata Journal. 2006;6(1):40-57.
60. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ: British Medical Journal. 1997;315(7109):629-34.
61. Tobias A. Assessing the influence of a single study in the meta-anyalysis estimate. Stata Technical Bulletin. 1999;8(47).
62. Clark BK, Sugiyama T, Healy GN, Salmon J, Dunstan DW, Owen N. Validity and reliability of measures of television viewing time and other non-occupational sedentary behaviour of adults: a review. Obesity Reviews. 2009;10(1):7-16.
63. Bryant MJ, Lucove JC, Evenson KR, Marshall S. Measurement of television viewing in children and adolescents: a systematic review. Obesity Reviews. 2007;8(3):197-209.
64. Jago R, Page A, Froberg K, Sardinha LB, Klasson-Heggebø L, Andersen LB. Screen-viewing and the home TV environment: The European Youth Heart Study. Preventive Medicine. 2008;47(5):525-9.
65. Ekelund U, Brage S, Froberg K, Harro M, Anderssen SA, Sardinha LB, et al. TV viewing and physical activity are independently associated with metabolic risk in children: the European Youth Heart Study. PLoS.Med. 2006;3(12):e488.
66. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and Management of the Metabolic Syndrome. Circulation. 2005;112(17):2735-52.
67. Ekelund U, Luan Ja, Sherar LB, Esliger DW, Griew P, Cooper A. Moderate to Vigorous Physical Activity and Sedentary Time and Cardiometabolic Risk Factors in Children and Adolescents. JAMA: The Journal of the American Medical Association. 2012;307(7):704-12.

68. Rubin DB. Multiple Imputation After 18+ Years. Journal of the American Statistical Association. 1996;91(434):473-89.
69. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Jr., Tudor-Locke C, et al. 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. Med Sci Sports Exerc. 2011.
70. Chasan-Taber S, Rimm EB, Stampfer MJ, Spiegelman D, Colditz GA, Giovannucci E, et al. Reproducibility and Validity of a Self-Administered Physical Activity Questionnaire for Male Health Professionals. Epidemiology. 1995;7(1):81-6.
71. Jacobs DR, Jr., Ainsworth BE, Hartman TJ, Leon AS. A simultaneous evaluation of 10 commonly used physical activity questionnaires. Med Sci Sports Exerc. 1993;25(1):81-91.
72. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. American Journal of Epidemiology. 1994;140(11):1016-9.
73. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992;135(10):1114-26.
74. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women. New England Journal of Medicine. 2001;345(11):790-7.
75. Greenland S. Dose-Response and Trend Analysis in Epidemiology: Alternatives to Categorical Analysis. Epidemiology. 1995;6(4):356-65.
76. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999;94(446):496-509.
77. Andersen LB, Henckel P. Maximal voluntary isometric strength in Danish adolescents 16-19 years of age. Eur J Appl Physiol Occup Physiol. 1987;56(1):83-9.
78. Essendrop M, Schibye B, Hansen K. Reliability of isometric muscle strength tests for the trunk, hands and shoulders. International Journal of Industrial Ergonomics. 2001;28(6):379-87.
79. Kolle E, Steene-Johannessen J, Andersen LB, Anderssen SA. Objectively assessed physical activity and aerobic fitness in a population-based sample of Norwegian 9-

and 15-year-olds. Scandinavian Journal of Medicine & Science in Sports. 2010;20(1):e41-e7.

80. Anderssen SA, Cooper AR, Riddoch C, Sardinha LB, Harro M, Brage S, et al. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. European Journal of Cardiovascular Prevention & Rehabilitation. 2007;14(4):526-31.
81. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. Circulation. 2002;106(25):3143.
82. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.
83. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr. 2004;144(1):47-55.
84. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J. 2011;32(14):1704-8.
85. Royston P. Multiple imputation of missing values. Stata Journal. 2004;4:227-41.
86. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine. 2011;30(4):377-99.
87. Centers for Disease C, Prevention. Crude and Age-Adjusted Incidence of Diagnosed Diabetes per 1,000 Population Aged 18-79 Years. United States, 1980-2007.[http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm%5D. 2011.
88. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart Disease and Stroke Statistics--2011 Update: A Report From the American Heart Association. Circulation. 2011;123(4):e18-209.
89. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: final data for 2007. Natl Vital Stat Rep. 2010;58(19):1-136.
90. Hardy LL, Booth ML, Okely AD. The reliability of the Adolescent Sedentary Activity Questionnaire (ASAQ). Preventive Medicine. 2007;45(1):71-4.
91. Rey-López JP, Ruiz JR, Ortega FB, Verloigne M, Vicente-Rodriguez G, Gracia-Marco L, et al. Reliability and validity of a screen time-based sedentary behaviour

questionnaire for adolescents: The HELENA study. The European Journal of Public Health. 2012;22(3):373-7.

92. Schmitz KH, Harnack L, Jacobs Jr DR, Gao S, Lytle LA, Coevering PV, et al. Reliability and Validity of a Brief Questionnaire to Assess Television Viewing and Computer Use. Journal of School Health. 2004;74(9):370-7.
93. Vereecken CA, Todd J, Roberts C, Mulvihill C, Maes L. Television viewing behaviour and associations with food habits in different countries. Public Health Nutrition. 2006;9(02):244-50.
94. Schwartz B, Jacobs DR, Moran A, Steinberger J, Hong C-P, Sinaiko AR. Measurement of Insulin Sensitivity in Children: Comparison between the euglycemic-hyperinsulinemic clamp and surrogate measures. Diabetes Care. 2008;31(4):783-8.
95. Mari A, Pacini G, Brazzale AR, Ahrén B. Comparative evaluation of simple insulin sensitivity methods based on the oral glucose tolerance test. Diabetologia. 2005;48(4):748-51.
96. Wallace TM, Levy JC, Matthews DR. Use and Abuse of HOMA Modeling. Diabetes Care. 2004;27(6):1487-95.
97. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabet Med. 1999;16(5):442-3.
98. Chapman CD, Benedict C, Brooks SJ, Birgir Schiöth H. Lifestyle determinants of the drive to eat: a meta-analysis. The American Journal of Clinical Nutrition. 2012;96(3):492-7.
99. Wilmot EG, Edwardson CL, Achana FA, Davies MJ, Gorely T, Gray LJ, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. Diabetologia. 2012;55(11):2895-905.
100. Ford ES, Caspersen CJ. Sedentary behaviour and cardiovascular disease: a review of prospective studies. International Journal of Epidemiology. 2012;41(5):1338-53.
101. Matthews CE, George SM, Moore SC, Bowles HR, Blair A, Park Y, et al. Amount of time spent in sedentary behaviors and cause-specific mortality in US adults. The American Journal of Clinical Nutrition. 2012;Jan 4. [Epub ahead of print].
102. Ford E. Combined television viewing and computer use and mortality from all-causes and diseases of the circulatory system among adults in the United States. BMC Public Health. 2012;12(1):70.

103. Inoue M, Iso H, Yamamoto S, Kurahashi N, Iwasaki M, Sasazuki S, et al. Daily Total Physical Activity Level and Premature Death in Men and Women: Results From a Large-Scale Population-Based Cohort Study in Japan (JPHC Study). Annals of Epidemiology. 2008;18(7):522-30.
104. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Med Sci Sports Exerc. 2009;41(5):998-1005.
105. Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, et al. Walking Compared with Vigorous Exercise for the Prevention of Cardiovascular Events in Women. New England Journal of Medicine. 2002;347(10):716-25.
106. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, et al. Leisure Time Spent Sitting in Relation to Total Mortality in a Prospective Cohort of US Adults. American Journal of Epidemiology. 2010;172(4):419-29.
107. van der Ploeg Hp CTKRJBEBA. SItting time and all-cause mortality risk in 222 497 australian adults. Archives of Internal Medicine. 2012;172(6):494-500.
108. Koster A, Caserotti P, Patel KV, Matthews CE, Berrigan D, Van Domelen DR, et al. Association of Sedentary Time with Mortality Independent of Moderate to Vigorous Physical Activity. PLoS ONE. 2012;7(6):e37696.
109. Robinson TN. Reducing Children's Television Viewing to Prevent Obesity. JAMA: The Journal of the American Medical Association. 1999;282(16):1561-7.
110. Epstein LH, Roemmich JN, Robinson JL, Paluch RA, Winiewicz DD, Fuerch JH, et al. A Randomized Trial of the Effects of Reducing Television Viewing and Computer Use on Body Mass Index in Young Children. Archives of Pediatrics Adolescent Medicine. 2008;162(3):239-45.
111. Paalanne NP, Korpelainen RI, Taimela SP, Auvinen JP, Tammelin TH, Hietikko TM, et al. Muscular fitness in relation to physical activity and television viewing among young adults. Med Sci Sports Exerc. 2009;41(11):1997-2002.
112. Fitzpatrick C, Pagani LS, Barnett TA. Early childhood television viewing predicts explosive leg strength and waist circumference by middle childhood. Int J Behav Nutr Phys Act. 2012;9(1):87.
113. Katzmarzyk PT, Malina RM, Song TMK, Bouchard C. Television viewing, physical activity, and health-related fitness of youth in the Québec family study. Journal of Adolescent Health. 1998;23(5):318-25.

114. Tucker LA. The relationship of television viewing to physical fitness and obesity. Adolescence. 1986;21(84):797-806.
115. Srikanthan P, Karlamangla AS. Relative Muscle Mass Is Inversely Associated with Insulin Resistance and Prediabetes. Findings from The Third National Health and Nutrition Examination Survey. Journal of Clinical Endocrinology & Metabolism. 2011.
116. Cheng YJ, Gregg EW, De Rekeneire N, Williams DE, Imperatore G, Caspersen CJ, et al. Muscle-Strengthening Activity and Its Association With Insulin Sensitivity. Diabetes Care. 2007;30(9):2264-70.
117. Janz KF, Dawson JD, Mahoney LT. Increases in Physical Fitness During Childhood Improve Cardiovascular Health During Adolescence: The Muscatine Study. Int J Sports Med. 2002;23(S1):15-21.
118. Benson AC, Torode ME, Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes. 2006;1(4):222-31.
119. Shaibi GQ, Cruz ML, Ball GD, Weigensberg MJ, Salem GJ, Crespo NC, et al. Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. Med Sci Sports Exerc. 2006;38(7):1208-15.
120. Benson AC, Torode ME, Fiatarone Singh MA. The effect of high-intensity progressive resistance training on adiposity in children: a randomized controlled trial. Int J Obes (Lond). 2008;32(6):1016-27.
121. Lee S, Bacha F, Hannon T, Kuk JL, Boesch C, Arslanian S. Effects of Aerobic Versus Resistance Exercise Without Caloric Restriction on Abdominal Fat, Intrahepatic Lipid, and Insulin Sensitivity in Obese Adolescent Boys: A Randomized, Controlled Trial. Diabetes. 2012;61(11):2787-95.
122. Cornelissen VA, Fagard RH, Coeckelberghs E, Vanhees L. Impact of Resistance Training on Blood Pressure and Other Cardiovascular Risk Factors. Hypertension. 2011;58(5):950-8.
123. Levine JA, Schleusner SJ, Jensen MD. Energy expenditure of nonexercise activity. The American Journal of Clinical Nutrition. 2000;72(6):1451-4.
124. Levine JA, Lanningham-Foster LM, McCrady SK, Krizan AC, Olson LR, Kane PH, et al. Interindividual Variation in Posture Allocation: Possible Role in Human Obesity. Science. 2005;307(5709):584-6.

125. Stephens BR, Granados K, Zderic TW, Hamilton MT, Braun B. Effects of 1 day of inactivity on insulin action in healthy men and women: interaction with energy intake. Metabolism. 2011;60(7):941-9.
126. Dunstan DW, Kingwell BA, Larsen R, Healy GN, Cerin E, Hamilton MT, et al. Breaking Up Prolonged Sitting Reduces Postprandial Glucose and Insulin Responses. Diabetes Care. 2012;35(5):976-83.
127. Dela F, Kjaer M. Resistance training, insulin sensitivity and muscle function in the elderly. Essays Biochem. 2006;42:75-88.
128. Hawley JA. Molecular responses to strength and endurance training: are they incompatible? Appl Physiol Nutr Metab. 2009;34(3):355-61.
129. LeBrasseur NK, Walsh K, Arany Z. Metabolic benefits of resistance training and fast glycolytic skeletal muscle. American Journal of Physiology - Endocrinology And Metabolism. 2011;300(1):E3-E10.
130. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JFP, Dela F. Strength Training Increases Insulin-Mediated Glucose Uptake, GLUT4 Content, and Insulin Signaling in Skeletal Muscle in Patients With Type 2 Diabetes. Diabetes. 2004;53(2):294-305.
131. Koskelo R, Vuorikari K, Hänninen O. Sitting and standing postures are corrected by adjustable furniture with lowered muscle tension in high-school students. Ergonomics. 2007;50(10):1643-56.
132. Katzmarzyk PT, Lee I-M. Sedentary behaviour and life expectancy in the USA: a cause-deleted life table analysis. BMJ Open. 2012;2(4).
133. Juneja H, Verma SK, Khanna GL. Isometric Strength and Its Relationship to Dynamic Performance: A Systematic Review. Journal of Exercise Science and Physiotherapy. 2010;6(2):60-9.
134. Roland KP, Jakobi JM, Jones GR. Does Yoga Engender Fitness in Older Adults? A Critical Review. Journal of Aging & Physical Activity. 2011;19(1):62-79.
135. Cruz-Ferreira A, Fernandes J, Laranjo L, Bernardo LM, Silva A. A Systematic Review of the Effects of Pilates Method of Exercise in Healthy People. Archives of Physical Medicine and Rehabilitation. 2011;92(12):2071-81.

List of appendences

Papers I–VI

Paper I

Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A meta-analysis. *JAMA: The Journal of the American Medical Association.* 2011;305(23):2448-55.

Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality

A Meta-analysis

Anders Grøntved, MPH, MSc
Frank B. Hu, MD, PhD

Context Prolonged television (TV) viewing is the most prevalent and pervasive sedentary behavior in industrialized countries and has been associated with morbidity and mortality. However, a systematic and quantitative assessment of published studies is not available.

Objective To perform a meta-analysis of all prospective cohort studies to determine the association between TV viewing and risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality.

Data Sources and Study Selection Relevant studies were identified by searches of the MEDLINE database from 1970 to March 2011 and the EMBASE database from 1974 to March 2011 without restrictions and by reviewing reference lists from retrieved articles. Cohort studies that reported relative risk estimates with 95% confidence intervals (CIs) for the associations of interest were included.

Data Extraction Data were extracted independently by each author and summary estimates of association were obtained using a random-effects model.

Data Synthesis Of the 8 studies included, 4 reported results on type 2 diabetes (175 938 individuals; 6428 incident cases during 1.1 million person-years of follow-up), 4 reported on fatal or nonfatal cardiovascular disease (34 253 individuals; 1052 incident cases), and 3 reported on all-cause mortality (26 509 individuals; 1879 deaths during 202 353 person-years of follow-up). The pooled relative risks per 2 hours of TV viewing per day were 1.20 (95% CI, 1.14-1.27) for type 2 diabetes, 1.15 (95% CI, 1.06-1.23) for fatal or nonfatal cardiovascular disease, and 1.13 (95% CI, 1.07-1.18) for all-cause mortality. While the associations between time spent viewing TV and risk of type 2 diabetes and cardiovascular disease were linear, the risk of all-cause mortality appeared to increase with TV viewing duration of greater than 3 hours per day. The estimated absolute risk differences per every 2 hours of TV viewing per day were 176 cases of type 2 diabetes per 100 000 individuals per year, 38 cases of fatal cardiovascular disease per 100 000 individuals per year, and 104 deaths for all-cause mortality per 100 000 individuals per year.

Conclusion Prolonged TV viewing was associated with increased risk of type 2 diabetes, cardiovascular disease, and all-cause mortality.

JAMA. 2011;305(23):2448-2455 www.jama.com

TELEVISION (TV) VIEWING IS THE most commonly reported daily activity apart from working and sleeping in many populations around the world.[1-3] On average, 40% of daily free time is occupied by TV viewing within several European countries[1] and 50% in Australia.[2] This corresponds to a daily TV viewing time of about 3.5 to 4.0 hours. In the United States, the average number of daily hours of TV viewing has recently been reported to be 5 hours.[3]

Beyond altering energy expenditure by displacing time spent on physical activities, TV viewing is associated with unhealthy eating (eg, higher intake of fried foods, processed meat, and sugar-sweetened beverages and lower intake of fruits, vegetables, and whole grains) in both children and adults.[4-7] Furthermore, TV viewing may be associated with the intake of foods and beverages that are advertised on TV[4] and could attract some individuals to begin smoking.[8]

Physical inactivity, various dietary factors, and smoking are well-established independent risk factors of type 2 diabetes, cardiovascular disease, and all-cause mortality. Because

CME available online at www.jamaarchivescme.com and questions on p 2476.

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TV viewing is the most prevalent and pervasive sedentary behavior, there is a great deal of interest in quantifying its independent association with health outcomes. However, a systematic and quantitative assessment of published studies is not available. Therefore, we conducted a meta-analysis to summarize all published prospective cohort studies to date on the incidence of type 2 diabetes, nonfatal or fatal cardiovascular disease, and all-cause mortality. Furthermore, we quantified the dose-response relationship of TV viewing with the risk of these health outcomes.

METHODS

Search Strategy

The meta-analysis was conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology.[9] We performed a systematic search of published studies in MEDLINE from 1970 to March 2011 and in EMBASE from 1974 to March 2011.

We used the following search terms without restrictions: *TV* or *television* or "*screen time*" and *diabetes* or *cardiovascular* or *myocardial* or *coronary* or *stroke* or *mortality* or *mortalities* or *death* or *fatal* and *risk* or *Cox* or *hazard* or "*survival analysis*" or *odds*. In addition, we reviewed the reference lists of retrieved articles to identify any studies that were not identified from the preliminary literature searches.

Inclusion Criteria

Studies were included in the meta-analysis if they met the following criteria: published in the English language, had a prospective design (cohort, case-cohort, and nested case-control), a study population that was healthy at baseline, and had estimates of relative risk (RR) or odds ratio with 95% confidence intervals (CIs) or reported data to calculate these.

Data Extraction

From each retrieved article, we extracted the following data: name of the first author, year of publication, country where the study was performed, specific outcomes, follow-up time, methods for assessment of outcome, proportion of men and women, total number of individuals, person-years of follow-up, number of cases, confounding factors that were adjusted for in the analysis, and the RRs or odds ratio estimates with corresponding 95% CIs. We extracted multivariable-adjusted estimates with and without adjustment for dietary variables and with and without adjustment for body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) or another obesity measure when available.

Data extraction was conducted independently by both authors (A.G. and F.B.H.) and any disagreements were resolved by consensus. In studies in which TV viewing was reported as hours per week or minutes per day, we converted this to hours per day. We pooled estimates of risk in increments of 2 hours of TV viewing per day. If a study did not report the association with TV viewing as a continuous variable, we estimated this using the method of generalized least squares for trend estimation described by Orsini et al.[10] For categories of TV viewing that were open (eg, 4-7 hours per day), we assigned the median values of TV viewing. If the upper bound in the highest category was not provided, we assumed that it had the same amplitude as the preceding category. This procedure also was performed for obtaining data for the dose-response meta-analysis. If the appropriate data were not obtainable, we requested the data from the study's investigators.

Statistical Analysis

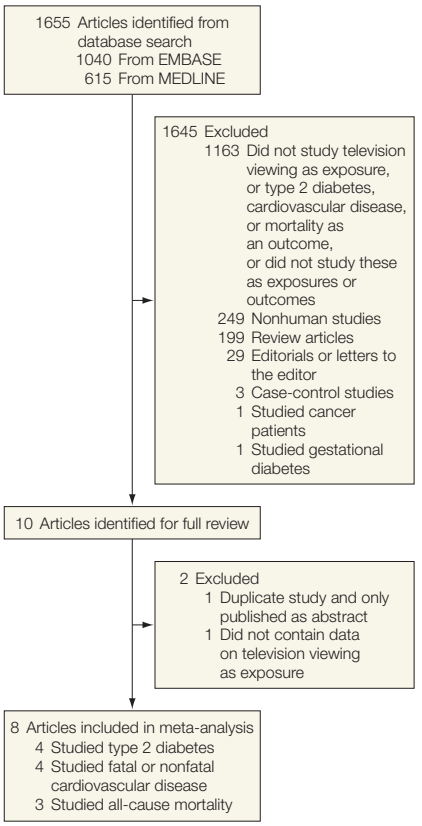
We pooled RR estimates (assuming a linear relationship of the natural logarithm of RR with increasing TV viewing time and 95% CIs) from each study separately for each outcome using a random-effects meta-analysis. We evaluated the statistical heterogeneity of the RRs by calculating the I^2 statistic[11]; publication bias was assessed by using the Egger asymmetry test.[12] Low, moderate, and high degrees of heterogeneity correspond to I^2 values of 25%, 50%, and 75%, respectively. Sensitivity analyses evaluated whether the results could have been affected markedly by a single study,[13] and were repeated using a fixed-effects model.

Because obesity is a putative mediator of the association between TV viewing and respective health outcomes, we included (when possible) multivariable-adjusted models that did not adjust for BMI or another obesity measure. Whenever possible, we also separately performed a meta-analysis on the multivariable-adjusted model with and then without adjustment for dietary variables and also with and then without BMI or other obesity measures to explore the possible mediating effect of diet, BMI, and obesity on the association of TV viewing with the study outcomes.

We then plotted the dose-response relationship based on the dose-response meta-analysis method described by Orsini et al,[10] using all available data points from each study. To flexibly plot the relationship of the natural logarithm of RRs with increasing TV viewing time without assuming linearity and to test if they were nonlinear, we added a quadratic term of TV viewing time; the changes in model fit were tested using the likelihood ratio test. For any nonlinear response, we proceeded to use piecewise regression with an inflection point based on the best goodness-of-fit model.[10]

We calculated absolute risk differences based on the obtained summary estimate and incidence rates from the general US population using the formula: risk difference = background incidence rate × (RR − 1). All statistical analyses were 2-sided and performed with Stata statistical software version 11 (StataCorp, College Station, Texas); an α level of .05 was chosen for significance.

Figure 1. Selection of Studies Included in the Meta-analysis



RESULTS

Literature Search

The results of the literature search are shown in FIGURE 1. We retrieved 1655 articles from our preliminary search. Of these, 10 articles were identified for full review (some reported analyses on >1 relevant outcome). There were 4 studies reporting results on type 2 diabetes, 6 studies reporting on fatal or nonfatal cardiovascular disease, and 4 studies reporting on all-cause mortality. After full review, 1 study on incident cardiovascular disease was excluded because it was only published as an abstract[14] (this study also was a duplicate of a fatal cardiovascular disease analysis). Another study reporting on both fatal cardiovascular disease and all-cause mortality was excluded due to lack of specific report on the association with TV viewing.[15]

Of the 10 studies, 8 were included in the meta-analysis. The study by Stamatakis et al[16] on all-cause mortality and cardiovascular disease reported associations of screen time including both TV viewing and other types of screen time such as video game playing and computer use. Because total screen time predominantly stems from TV viewing, we choose to include this study.

Study Characteristics

The characteristics of the included studies are shown in the TABLE. For type 2 diabetes (4 studies), the total number of individuals was 175 938 with 6428 incident cases during 1.1 million person-years of follow-up. For fatal or nonfatal cardiovascular disease (4 studies), the total number of individuals was 34 253 with 1052 incident cases; there was no indication of person-years at risk because 1 study[20] lacked that information. For all-cause mortality (3 studies), the total number of individuals was 26 509 with 1879 deaths during 202 353 person-years of follow-up. The mean (SD) follow-up duration was 8.5 (1.9) years for type 2 diabetes, 10.4 (7.4) years for fatal or nonfatal cardiovascular disease, and 6.8 (2.6) years for all-cause mortality. The number of potential confounding factors included in the multivariable-adjusted model varied (Table).

TV Viewing and Risk of Type 2 Diabetes

FIGURE 2 shows the results from the random-effects meta-analysis of the dose-response relationship between TV viewing and type 2 diabetes in the 4 studies. In the meta-analysis of the multivariable-adjusted estimates without adjustment for dietary variables, greater TV viewing time was associated with a higher risk of type 2 diabetes (pooled RR, 1.20 [95% CI, 1.14-1.27] per 2 hours of TV viewing time; $P<.001$) and a linear dose-response relationship was observed (FIGURE 3; $P=.08$ for nonlinear response; goodness-of-fit $\chi^2_{13}=20.5$, $P=.07$).

The corresponding absolute risk difference based on the most recent type 2 diabetes statistics[22] for the United States was estimated to be 176 cases per 100 000 individuals per year for every 2 hours of TV viewing per day. There was moderate heterogeneity between studies ($I^2=50.4\%$, $P=.11$). There was no statistical evidence of publication bias (Egger asymmetry test, $P=.21$).

Further adjusting for dietary variables slightly attenuated the risk estimate but an increased risk of type 2 diabetes remained with greater TV viewing time (pooled RR, 1.18 [95% CI, 1.12-1.25] per 2 hours of TV viewing time; $P<.001$). When individual studies were pooled with an additional adjustment for BMI or another obesity measure, the summary estimate was attenuated to 1.13 (95% CI, 1.08-1.18) per 2 hours of TV viewing time ($P<.001$).

TV Viewing and Risk of Fatal or Nonfatal Cardiovascular Disease

Longer duration of TV viewing time was associated with an increased risk of fatal or nonfatal cardiovascular disease (RR, 1.15 [95% CI, 1.06-1.23] per 2 hours of TV viewing per day; $P<.001$; Figure 2). A linear dose-response relationship was observed (Figure 3; $P=.37$ for nonlinear response; goodness-of-fit $\chi^2_{14}=22.6$, $P=.07$). The corresponding absolute risk difference based on the most recent American Heart Association cardiovascular disease mortality rate statistics for the United States[23] was estimated to be 38 cases of fatal cardiovascular disease per 100 000 individuals per year for every 2 hours of TV viewing per day. There was no heterogeneity in the individual risk estimates for fatal or nonfatal cardiovascular disease ($I^2=0\%$, $P=.73$) and there was no evidence of publication bias ($P=.72$).

Only the study by Wijndaele et al[21] reported estimates with and without adjustment for dietary variables (total energy intake) and BMI, respectively. The 3 other studies[16,19,20] included dietary variables and BMI or waist circumference in their multivariable-adjusted model. When we repeated the meta-analysis and included the diet-adjusted point estimate from Wijndaele

Table. Characteristics of the Studies Included in the Meta-analysis

Source and Study Location	Ratio of Males to Females, %	Age at Baseline, y	Follow-up, y	Total No. of Individuals/ Person-Years	No. of Cases	Outcome Assessment	Adjustment for Confounders
Type 2 diabetes							
Hu et al,[7] 2001; United States	100:0	40-75	10[a]	37 918/347 040	1058	Self-report	Age, length of smoking, parental history of diabetes, alcohol consumption, total physical activity; and intakes of saturated fat, monounsaturated fat, polyunsaturated fat, *trans*-fatty acids, and cereal fiber
Hu et al,[6] 2003; United States	0:100	30-55	6[a]	68 497/396 900	1515	Self-report	Age, hormone use, family history of diabetes, alcohol consumption, total physical activity, glycemic load; and intakes of polyunsaturated fatty acid, cereal fiber, and *trans*-fatty acids
Krishnan et al,[17] 2009; United States	0:100	21-69	10[a]	45 668/182 994	2928	Self-report	Age, family history of diabetes, years of education, family income, marital status, smoking status, alcohol consumption, energy intake, coffee consumption, vigorous physical activity, and walking as physical activity
Ford et al,[18] 2010; Germany	38:62	35-65	7.8[b]	23 855/156 358	927	Self-report	Age, sex, educational status, occupational physical activity, smoking status, alcohol consumption, and leisure-time physical activity
Cardiovascular disease (fatal or nonfatal)							
Dunstan et al,[19] 2010; Australia	44:56	≥25	6.6[c]	8800/58 087	87	Registry	Age, sex, smoking status, educational level, total energy intake, alcohol intake, diet-quality index, waist circumference, hypertension, total cholesterol, HDL cholesterol, triglycerides, lipid-lowering medication use, and glucose-tolerance status
Warren et al,[20] 2010; United States	100:0	20-89	21[a]	7744/NA	377	Registry	Age, physical activity, smoking status, alcohol consumption, BMI, family history of cardiovascular disease, hypertension, diabetes, and hypercholesterolemia
Stamatakis et al,[16] 2011; Scotland	43:57	≥35	4.3 (0.5)[d]	4512/19 364	215	Registry	Age, sex, BMI, smoking status, marital status, ethnicity, social class, long-standing illness, occupational physical activity, physician-diagnosed diabetes and hypertension, and moderate and vigorous physical activity
Wijndaele et al,[21] 2011; United Kingdom	43:57	45-79	9.5 (1.6)[d]	13 197/124 902	373	Registry	Age, sex, educational level, smoking status, alcohol consumption, medication for hypertension, medication for dyslipidemia, baseline history of diabetes, family history of cardiovascular disease, family history of cancer, total physical activity energy expenditure, and total energy intake
All-cause mortality							
Dunstan et al,[19] 2010; Australia	44:56	≥25	6.6[c]	8800/58 087	284	Registry	Age, sex, smoking status, education, total energy intake, alcohol intake, diet-quality index, waist circumference, hypertension, total cholesterol, HDL cholesterol, triglycerides, lipid-lowering medication use, and glucose tolerance status
Stamatakis et al,[16] 2011; Scotland	43:57	≥35	4.3 (0.5)[d]	4512/19 364	325	Registry	Age, sex, BMI, smoking status, marital status, ethnicity, social class, long-standing illness, occupational physical activity, physician-diagnosed diabetes and hypertension, and moderate and vigorous physical activity
Wijndaele et al,[21] 2011; United Kingdom	43:57	45-79	9.5 (1.6)[d]	13 197/124 902	1270	Registry	Age, sex, educational level, smoking status, alcohol consumption, medication for hypertension, medication for dyslipidemia, baseline history of diabetes, family history of cardiovascular disease, family history of cancer, total physical activity energy expenditure, and total energy intake

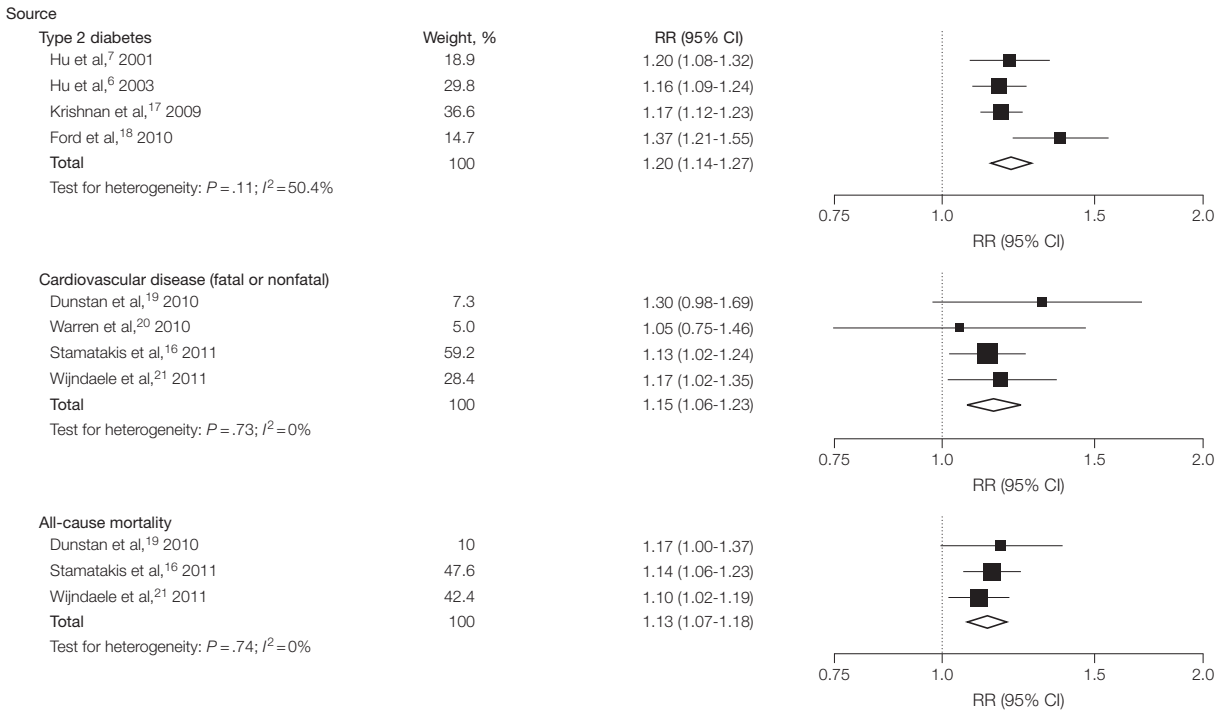
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL, high-density lipoprotein; NA, data not available.
[a] Either mean or median follow-up time were not specified by the study's authors.
[b] Value expressed as mean.
[c] Value expressed as median.
[d] Value expressed as mean (SD).

et al,[21] the results were not substantially changed (pooled RR, 1.15 [95% CI, 1.07-1.25] per 2 hours of TV viewing time per day; $P<.001$). When the primary meta-analysis was repeated using the BMI-adjusted estimate from Wijndaele et al,[21] the point estimate was not substantially attenuated (pooled RR, 1.14 [95% CI, 1.06-1.23] per 2 hours of TV viewing time per day; $P=.001$).

TV Viewing and Risk of All-Cause Mortality

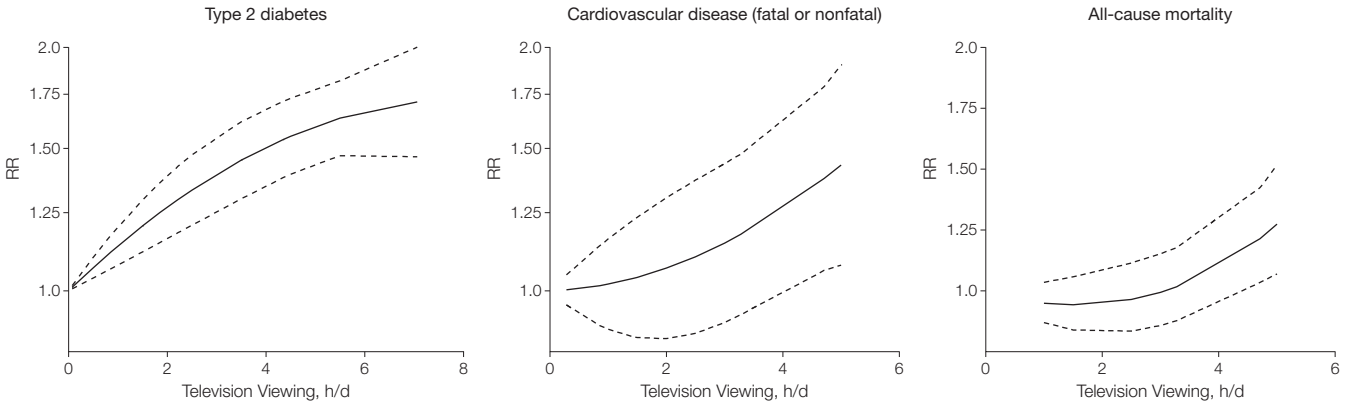
The results from the random-effects meta-analysis of TV viewing with the risk of all-cause mortality are shown

Figure 2. Risk of Type 2 Diabetes, Cardiovascular Disease, and All-Cause Mortality



The summary estimates were obtained using a random-effects model. The data markers indicate the adjusted relative risks (RRs) per 2 hours of television viewing per day. The size of the data markers indicates the weight of the study. The diamond data markers indicate the pooled RRs. CI indicates confidence interval.

Figure 3. Dose-Response Relationship Between Television Viewing and Risk of Type 2 Diabetes, Cardiovascular Disease, All-Cause Mortality



Dotted lines represent the 95% confidence intervals for the fitted trend. The dose-response relationship plot between television (TV) viewing (hours per day) and risk of type 2 diabetes (4 studies), cardiovascular disease (4 studies), and all-cause mortality (3 studies) was estimated with random-effects meta-regression,[10] which allowed for a nonlinear response by including a quadratic term of TV viewing time. The test for a nonlinear relationship was only significant for all-cause mortality ($P=.007$). In subsequent piecewise regression, the best model fit was obtained at an inflection point of 3 hours of TV viewing per day ($P=.01$ for difference in slopes).

in Figure 2. Greater TV viewing time was associated with an increased risk of all-cause mortality (pooled RR, 1.13 [95% CI, 1.07-1.18] per 2 hours of TV viewing time per day; $P<.001$). The corresponding absolute risk difference based on the most recent US mortality rate statistics[24] was estimated to be 104 deaths per 100 000 individuals per year for every 2 hours of TV viewing per day. No statistical heterogeneity between studies was observed ($I^2=0\%$, $P=.74$) and we observed no evidence of publication bias (Egger asymmetry test, $P=.67$). The test for a nonlinear dose-response relationship was significant (likelihood ratio test, $P=.007$), suggesting curvature in the relationship (Figure 3).

In piecewise regression analysis, we obtained the best fit at an inflection point of 3 hours of TV viewing per day ($P=.01$ for difference in slopes). There was no association for up to 3 hours of TV viewing time per day with all-cause mortality. However, the RR was 1.30 (95% CI, 1.06-1.56) for greater than 3 hours of TV viewing time per day (goodness-of-fit $\chi^2_5=4.8$, $P=.45$).

Only the study by Wijndaele et al[21] reported estimates with additional adjustment for total energy intake and BMI. When the primary meta-analysis was repeated using the adjusted point estimate for energy intake from Wijndaele et al,[21] the pooled RR was 1.13 (95% CI, 1.07-1.19) per 2 hours of TV viewing time per day. When the primary meta-analysis was repeated using the BMI-adjusted point estimate from Wijndaele et al,[21] the pooled RR was 1.12 (95% CI, 1.06-1.18) per 2 hours of TV viewing time per day.

Sensitivity Analysis

The summary estimates were consistent when analyses were repeated using a fixed-effects model (eFigure at http://www.jama.com). Omitting 1 study at a time and recalculating the pooled RRs for the remainder of the studies showed that none of the individual studies substantially influenced the pooled RR for any of the outcomes (eTable at http://www.jama.com).

COMMENT

Our results from the meta-analysis of prospective cohort studies suggest that TV viewing is consistently associated with higher risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality. We observed RRs of 1.20 for type 2 diabetes, 1.15 for cardiovascular disease, and 1.13 for all-cause mortality per every 2-hour increase in TV viewing per day. Based on incidence rates in the United States, we estimated that the absolute risk difference (cases per 100 000 individuals per year) per 2 hours of TV viewing per day was 176 for type 2 diabetes, 38 for fatal cardiovascular disease, and 104 for all-cause mortality.

The dose-response analysis revealed a linear increase in risk with the number of hours per day of TV viewing for both type 2 diabetes and cardiovascular disease; the association with all-cause mortality appeared stronger with TV viewing time of greater than 3 hours per day. However, more studies are needed on all-cause mortality to quantify with greater confidence the nature of the relationship with TV viewing.

There were some limitations to this meta-analysis. First, although not suggested by the formal statistical tests we undertook, there is still a possibility of publication bias considering that the tests were likely to be underpowered. Second, the relatively small number of studies limited our ability to identify subgroups of individuals who were more susceptible to the reported relationships. The small number of studies also limited our ability to determine whether heterogeneity in summary estimates was explained by factors related to study quality.

Third, we cannot exclude the possibility of residual confounding and bias due to misclassification. Although the included studies attempted to control for various known risk factors, the possibility of residual or unmeasured confounding cannot be ruled out. Fourth, although all of the included studies excluded participants with chronic disease at baseline, it is still possible that reverse causality may contribute to some of the associations reported herein if participants with subclinical stages of disease become more sedentary. Fifth, in all of the included studies, the assessment of TV viewing relied on self-report at baseline except for the study by Hu et al[7] and Krishnan et al,[17] in which self-report information was obtained on 5 occasions. Single-point measurement increases the chance of random-measurement error, which may underestimate the reported associations. Sixth, not all available studies controlled properly for physical activity.

Appropriate control for physical activity in an analysis with TV viewing as exposure can be performed using the isotemporal substitution model because TV viewing will displace time spent on other activities.[25] Such activities could be sleeping, physical activity at different intensities, or other activities (eg, reading). Future studies should consider several displacement options to further explore the influence of TV viewing time on health outcomes. Finally, unpublished data, non-English-language studies, and missed studies may exist and may have influenced our results.

Strengths of this study include large sample sizes, long durations of follow-up, and well-established prospective studies. In addition, our pooled estimates were based on prospective analyses with detailed adjustment for a wide range of confounding variables.

It is biologically plausible that prolonged TV viewing is associated with type 2 diabetes, cardiovascular disease, and all-cause mortality. Numerous prospective studies have reported associations of TV viewing with biological risk factors for these outcomes including obesity,[6,26,27] adverse lipid levels,[27] and clustered cardiovascular risk[28]; however, some studies did not report these associations.[29-31] Furthermore, associations of sedentary behaviors analogous to TV viewing (eg, sitting during work or while driving) with type 2 diabetes,[6] fatal or nonfatal

cardiovascular disease,[32] fatal cardiovascular disease,[33,34] and all-cause mortality[33,34] have been reported in cohort studies. Experimental studies specifically increasing exposure to inactivity are difficult to perform in humans; however, one study[35] showed detrimental changes in insulin sensitivity and postprandial lipid metabolism in participants who markedly reduced their daily steps to about 1500 per day during a 2-week period.

Three randomized controlled trials have shown beneficial effects of reducing TV viewing time. One randomized school-based study of 9-year-old children (N=192) found that reducing time of TV viewing and video game playing slowed increases in BMI and decreased the number of meals eaten in front of the TV but was not associated with change in self-reported physical activity.[36]

Another study of 70 children with BMIs above the 75th percentile showed that reducing TV viewing and computer time by 50% over 2 years resulted in a significant reduction of BMI and energy intake but did not increase objectively measured physical activity.[37] The third study was conducted in 36 overweight or obese adults and it did not find a significantly greater change in energy intake or BMI after restricting TV viewing time by 50% over a 3-week period; however, a significant increase in objectively measured energy expenditure was observed.[38] These short-term experimental studies suggest that reducing TV viewing time may lead to improvement in diet, physical activity, or BMI.

Because TV viewing is often accompanied by concurrent intake of foods[4,5] and food advertising on TV may promote an unhealthy diet,[39] it is possible that some of the associations reported herein are explained by diet. We attempted to explore whether these associations were mediated by diet and observed a small attenuation of effect estimates for type 2 diabetes but not for cardiovascular disease or all-cause mortality after pooling the available estimates with additional adjustment for dietary variables.

Because positive associations with TV viewing were observed in European, Australian, and US populations, who are subject to different amounts and types of food advertisements on TV, we do not believe that the associations are completely explained by changes in dietary behaviors induced by TV advertisement. However, we found that adjustment for BMI attenuated the association between TV viewing and the risk of type 2 diabetes.

Additional research quantifying the mediating influence of diet and physical inactivity is warranted. Future research also should assess the association of prolonged daily use of new media devices on energy balance and chronic disease risk.

In conclusion, findings from this meta-analysis of prospective studies suggest that longer duration of TV viewing time is consistently associated with higher risk of type 2 diabetes, fatal or nonfatal cardiovascular disease, and all-cause mortality. Further study is needed to determine whether reducing prolonged TV viewing can prevent chronic disease morbidity and mortality.

Author Contributions: Mr Grøntved had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Grøntved, Hu.
Acquisition of data: Grøntved, Hu.
Analysis and interpretation of data: Grøntved, Hu.
Drafting of the manuscript: Grøntved, Hu.
Critical revision of the manuscript for important intellectual content: Grøntved, Hu.
Statistical analysis: Grøntved.
Obtained funding: Grøntved, Hu.
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REFERENCES

1. Office for Official Publications of the European Communities. Time use at different stages of life: results from 13 European countries, July 2003. http://epp.eurostat.ec.europa.eu/cache/ITY_OFFPUB/KS-CC-03-001/EN/KS-CC-03-001-EN.PDF. Accessibility verified May 16, 2011.
2. Australian Bureau of Statistics. *How Australians Use Their Time.* Canberra: Commonwealth of Australia; 2008.
3. Nielsen Co. TV usage trends: Q3 and Q4 2010. http://www.nielsen.com/content/dam/corporate/us/en/reports-downloads/2011-Reports/State%20of%20the%20Media%20TV%20Q3%20Q4%202010.pdf. Accessibility verified May 16, 2011.
4. Wiecha JL, Peterson KE, Ludwig DS, Kim J, Sobol A, Gortmaker SL. When children eat what they watch: impact of television viewing on dietary intake in youth. *Arch Pediatr Adolesc Med*. 2006;160(4):436-442.
5. Vereecken CA, Todd J, Roberts C, Mulvihill C, Maes L. Television viewing behaviour and associations with food habits in different countries. *Public Health Nutr*. 2006;9(2):244-250.
6. Hu FB, Li TY, Colditz GA, Willett WC, Manson JE. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA*. 2003;289(14):1785-1791.
7. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med*. 2001;161(12):1542-1548.
8. Gidwani PP, Sobol A, DeJong W, Perrin JM, Gortmaker SL. Television viewing and initiation of smoking among youth. *Pediatrics*. 2002;110(3):505-508.
9. Stroup DF, Berlin JA, Morton SC, et al; Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012.
10. Orsini N, Rino B, Sander G. Generalized least squares for trend estimation of summarized dose-response data. *Stata J*. 2006;6(1):40-57.
11. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
13. Tobias A. Assessing the influence of a single study in the meta-analysis estimate. *Stata Tech Bull*. 1999;47:15-17.
14. Wijndaele K, Brage S, Besson H, et al. Television viewing time and incident cardiovascular disease: prospective population-based study (EPIC Norfolk). *Obes Rev*. 2010;11(suppl 1):305.
15. Leitzmann MF, Park Y, Blair A, et al. Physical activity recommendations and decreased risk of mortality. *Arch Intern Med*. 2007;167(22):2453-2460.
16. Stamatakis E, Hamer M, Dunstan DW. Screen-based entertainment time, all-cause mortality, and cardiovascular events: population-based study with ongoing mortality and hospital events follow-up. *J Am Coll Cardiol*. 2011;57(3):292-299.
17. Krishnan S, Rosenberg L, Palmer JR. Physical activity and television watching in relation to risk of type 2 diabetes: the Black Women's Health Study. *Am J Epidemiol*. 2009;169(4):428-434.
18. Ford ES, Schulze MB, Kröger J, Pischon T, Bergmann MM, Boeing H. Television watching and incident diabetes: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam Study. *J Diabetes*. 2010;2(1):23-27.
19. Dunstan DW, Barr ELM, Healy GN, et al. Televi-

sion viewing time and mortality: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). *Circulation*. 2010;121(3):384-391.
20. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc*. 2010;42(5):879-885.
21. Wijndaele K, Brage S, Besson H, et al. Television viewing time independently predicts all-cause and cardiovascular mortality: the EPIC Norfolk study. *Int J Epidemiol*. 2011;40(1):150-159.
22. US Centers for Disease Control and Prevention. Crude and age-adjusted incidence of diagnosed diabetes per 1,000 population aged 18-79 years, United States, 1980-2009. http://www.cdc.gov/diabetes/statistics/incidence/fig2.htm. Accessibility verified May 16, 2011.
23. Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011; 123(4):e18-e209.
24. Xu J, Kochanek K, Murphy S, Tejada-Vera B. Deaths: final data for 2007. *Natl Vital Stat Rep*. 2010; 58(19):1-136.
25. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. *Am J Epidemiol*. 2009; 170(4):519-527.
26. Parsons TJ, Manor O, Power C. Television viewing and obesity: a prospective study in the 1958 British birth cohort. *Eur J Clin Nutr*. 2008;62(12):1355-1363.
27. Jakes RW, Day NE, Khaw KT, et al. Television viewing and low participation in vigorous recreation are independently associated with obesity and markers of cardiovascular disease risk: EPIC-Norfolk population-based study. *Eur J Clin Nutr*. 2003;57(9):1089-1096.
28. Wijndaele K, Healy GN, Dunstan DW, et al. Increased cardiometabolic risk is associated with increased TV viewing time. *Med Sci Sports Exerc*. 2010; 42(8):1511-1518.
29. Ekelund U, Brage S, Griffin SJ, Wareham NJ; ProActive UK Research Group. Objectively measured moderate- and vigorous-intensity physical activity but not sedentary time predicts insulin resistance in high-risk individuals. *Diabetes Care*. 2009;32(6):1081-1086.
30. Beunza JJ, Martínez-González MA, Ebrahim S, et al. Sedentary behaviors and the risk of incident hypertension: the SUN cohort. *Am J Hypertens*. 2007; 20(11):1156-1162.
31. Fung TT, Hu FB, Yu J, et al. Leisure-time physical activity, television watching, and plasma biomarkers of obesity and cardiovascular disease risk. *Am J Epidemiol*. 2000;152(12):1171-1178.
32. Manson JE, Greenland P, LaCroix AZ, et al. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med*. 2002;347(10):716-725.
33. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Med Sci Sports Exerc*. 2009;41(5):998-1005.
34. Weller I, Corey P. The impact of excluding non-leisure energy expenditure on the relation between physical activity and mortality in women. *Epidemiology*. 1998;9(6):632-635.
35. Olsen RH, Krogh-Madsen R, Thomsen C, Booth FW, Pedersen BK. Metabolic responses to reduced daily steps in healthy nonexercising men. *JAMA*. 2008; 299(11):1261-1263.
36. Robinson TN. Reducing children's television viewing to prevent obesity: a randomized controlled trial. *JAMA*. 1999;282(16):1561-1567.
37. Epstein LH, Roemmich JN, Robinson JL, et al. A randomized trial of the effects of reducing television viewing and computer use on body mass index in young children. *Arch Pediatr Adolesc Med*. 2008; 162(3):239-245.
38. Otten JJ, Jones KE, Littenberg B, Harvey-Berino J. Effects of television viewing reduction on energy intake and expenditure in overweight and obese adults: a randomized controlled trial. *Arch Intern Med*. 2009; 169(22):2109-2115.
39. Harris JL, Bargh JA, Brownell KD. Priming effects of television food advertising on eating behavior. *Health Psychol*. 2009;28(4):404-413.

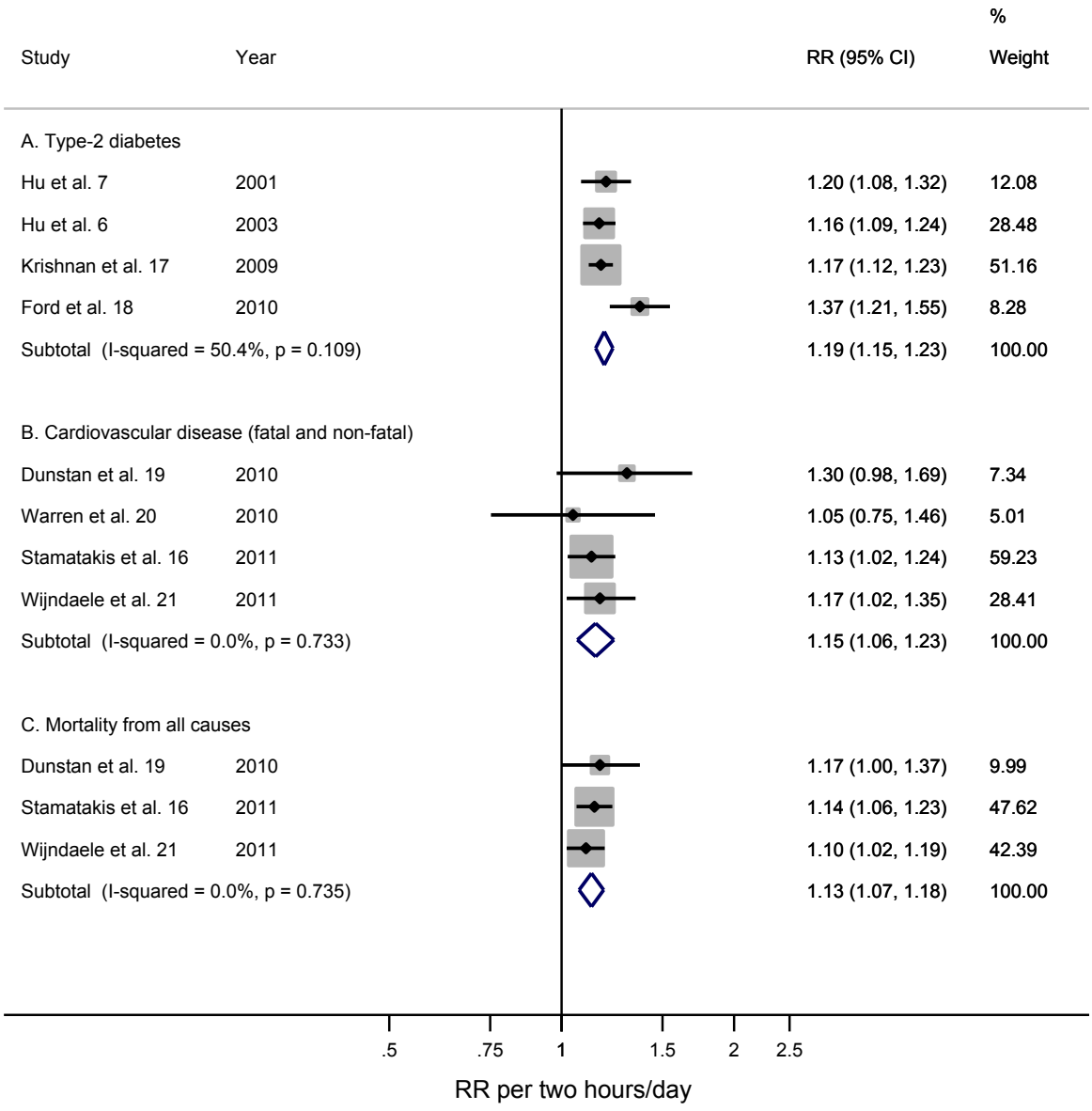
Every nail driven should be as another rivet in the machine of the universe, you carrying on the work.

—Henry David Thoreau (1817-1862)

eTable. Influence analysis of single studies on summary estimate (random effect model).

Study	**Beta (summary)**	**95% CI**
Type-2 diabetes	1.20	1.14 ; 1.27
Hu et al. 2001	1.21	1.12 ; 1.30
Hu et al. 2003	1.23	1.13 ; 1.33
Krishnan et al. 2009	1.23	1.12 ; 1.34
Ford et al. 2010	1.17	1.13 ; 1.21
CVD (fatal/non-fatal)	1.15	1.06 ; 1.23
Dunstan et al. 2010	1.14	1.05 ; 1.22
Warren et al. 2009	1.15	1.06 ; 1.24
Stamatakis et al. 2011	1.17	1.05 ; 1.31
Wijndaele et al. 2011	1.14	1.04 ; 1.24
Mortality from all-causes	1.13	1.07 ; 1.19
Dunstan et al. 2010	1.12	1.07 ; 1.18
Stamatakis et al. 2011	1.12	1.04 ; 1.20
Wijndaele et al. 2011	1.15	1.07 ; 1.22

eFigure. Pooled estimate of RR and 95% CI for risk of type-2 diabetes (A), fatal or non-fatal cardiovascular disease (B), and mortality from all-causes (C) respectively using a fixed effect model.



Squares indicate adjusted RRs per two hour TV viewing/day in each study and its size is proportional to the percent weight from each study in the meta-analysis. Horizontal lines indicate their 95% CIs. The unshaded diamond is the pooled RR with 95% CI.

Paper II

Grøntved A, Ried-Larsen M, Møller NC, Kristensen PL, Wedderkopp N, Froberg K, Hu FB, Ekelund U, Andersen LB. Youth screen time behaviour is associated with cardiovascular risk in young adulthood (The European Youth Heart Study). *European Journal of Preventive Cardiology*. 2012;(Epub ahead of print).

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Youth screen-time behaviour is associated with cardiovascular risk in young adulthood: the European Youth Heart Study

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Abstract

Aims: We prospectively examined the association of TV viewing, computer use, and total screen time in adolescence, and change in these behaviours, with cardiovascular disease (CVD) risk factors in young adulthood.

Methods and results: This was a prospective cohort study among Danish men and women ($n = 435$) followed for up to 12 years. Adiposity, blood pressure (BP), triglycerides, high-density lipoprotein (HDL), glucose, insulin, and self-reported TV viewing and computer use were obtained in adolescence and in young adulthood. A continuous metabolic syndrome z-score was calculated as the sum of standardized values of each risk factor (inverse of HDL). In multivariable-adjusted analyses, TV viewing and total screen time in adolescence were positively associated with adiposity, triglycerides, and metabolic syndrome z-score in young adulthood ($p < 0.05$). Individuals who increased their TV viewing, computer use, or total screen time with more than 2 hours/day from adolescence to young adulthood had 0.90 (95% CI 0.12 to 1.69), 0.95 (95% CI 0.01 to 1.88), and 1.40 (95% CI 0.28 to 2.51) kg/m^2 higher body mass index, respectively, in young adulthood compared with individuals who remained stable or decreased their viewing time. Insulin and metabolic syndrome z-scores were also higher among individuals who increased their TV viewing, computer use, or total screen time more than 2 hours/day compared with individuals who remained stable or decreased their viewing time ($p < 0.05$).

Conclusions: Prolonged TV viewing and total screen time during leisure time in adolescence, and increases in these behaviours, are associated with unfavourable levels of several cardiovascular risk factors in young adulthood.

Keywords

Cardiovascular risk, computer, obesity, screen time, television

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Introduction

TV viewing and computer use are common daily activities during leisure time among children, adolescents, and adults in Western countries.[1,2] Among adults, prolonged TV viewing and unspecified screen-viewing time have been consistently associated with greater risk of chronic diseases, premature death, and raised levels of cardiovascular risk factors independent of moderate and vigorous physical activity level (MVPA).[3–6] More recently, organizational and national recommendations for sedentary behaviours including screen time for

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children and adolescents have emerged.[7–9] Some of these recommendations state that children and adolescents should limit their recreational screen time to no more than 2 hours/day to minimize health risks.[7,8,10] The evidence from prospective studies to support these specific time limits is weak, and it is unknown if time spent on TV viewing and computer use each are independently associated with cardiovascular outcomes. Furthermore, the evidence that childhood or youth screen-viewing time are associated with adult cardiovascular health is scarce.[10–12] To extend the evidence that screen-viewing time during youth have health effects later in life, we aimed to examine the association of TV viewing, computer use, and total leisure screen-viewing time in adolescence with cardiovascular risk factors in young adulthood among Danish men and women participating in the European Youth Heart Study (EYHS) with up to 12 years of follow up. We also examined the influence of changes in viewing time on cardiovascular risk in young adulthood.

Methods

Design

The EYHS is an international population-based multicentre study that addresses cardiovascular disease (CVD) risk factors in children and adolescents.[13] The current study is based on the Danish cohort. In this study, a random sample of 658 15-year-old adolescents were invited to participate in 1997–98, of whom 429 (65%) agreed to take part in the study. In 2003–04, another random sample of 771 15-year-old adolescents was invited of whom 444 (58%) agreed to take part. In 2009–10, a 6- or 12-year follow up was conducted where all originally invited participants from 1997–98 and 2003–04 were invited again. The eligible cohort for the current analyses was 435 individuals who had complete data on exposures and outcomes (244 individuals with 6-year follow up and 191 individuals with 12-year follow up). The study was approved by the local scientific ethics committee and all participants gave informed consent to participate.

Television viewing, computer use, and total screen time

At baseline and follow up, TV viewing and computer use time during leisure was obtained by self-report. In both instances, this was done using a computer-based questionnaire.[13] At baseline, two questions were asked about the amount of time viewing TV (before and after school).[14] From these two questions, a summary variable of daily TV viewing time variable in adolescence was constructed (hours/day). Frequency of eating while viewing TV (5-point scale) was also asked. Daily time spent using computer in adolescence was asked in one question. At follow up the participants were asked to report their TV viewing time (hours and minutes) in the morning, afternoon, and evening. Again, a summary variable for daily TV viewing (hours/day) in young adulthood was constructed. Participants were asked about their time spent using a computer during leisure time (hours/day and min/day) separately for surfing the internet, playing games, and other tasks (i.e. word processing). From response to these questions, a summary variable for daily computer use was constructed (hours/day). A total screen time variable (hours/day) was created by summarizing TV viewing and computer use in adolescence and young adulthood, respectively.

Other covariates

Monthly frequency of soft drinks, fruit, and vegetable intake were obtained by self-report in adolescence. Family history of CVD (paternal or maternal, yes/no) and parental educational level were obtained by parental self-report. Parental educational status was defined according to the International Standard Classification of Education (ISCED) (UNESCO 1997). However, as the details obtained of the description of education was insufficient, the ISCED 7-point scale was combined into three new groups (1 = level 1–2; 2 = level 3–4; and 3 = level 5–7). Current smoking status (yes/no) was obtained in young adulthood. MVPA and sedentary time in adolescence was assessed using accelerometry with data reduction as described previously.[15] An output >2000 counts/min (equivalent to walking about 4 km/h) was defined as MVPA and an output <100 count/min was defined as sedentary. MVPA and sedentary time were expressed as continuous variables as percentage of total registered time.

Cardiovascular risk factors

Height, weight, and waist circumference (WC) were measured using standard anthropometric procedures. Fasting blood samples (overnight) were taken in the morning from the antecubital vein. Samples were aliquoted and separated within 30 min, and then stored at −80°C until they were transported to a WHO-certified laboratory in Bristol and Cambridge (UK) for analysis at baseline and in Cambridge at follow up. Samples were analysed for serum glucose, insulin, HDL cholesterol, and triglyceride. Triglyceride was analysed using the lipase/glycerol kinase/glycerol phosphate oxidase enzymatic method. HDL was analysed using the homogeneous polyanion/cholesterol esterase/oxidase enzymic method. Glucose was analysed using the hexokinase method. Blood lipids and glucose were

measured on an Olympus AU600 autoanalyser (Olympus Diagnostica, Germany) at baseline and on a Dade Behring Dimension RxL autonalyser (Siemens Healthcare, UK) at follow up. Insulin was analysed using enzyme immunoassay (microtitre plate format; Dako Diagnostics, http://www.dako.co.uk, at baseline; and 1235 AutoDELFIA automatic immunoassay, Wallac Oy, Finland at follow up). Between-laboratory correlations in lipids, glucose, and insulin for 30 randomly selected samples analysed at both laboratories were 0.94–0.98 at baseline.[14]

Resting BP was measured with a Dinamap paediatric and adult neonatal vital signs monitor (model XL; Critikron, Tampa, FL, USA) using an appropriate cuff size. Five measurements were taken at 2-min intervals with the mean of the final three measurements used in all analyses. Prior to measurements individuals were resting for 5 min while seated.

We calculated a continuous metabolic syndrome z-score to preserve statistical power and because the number of incident cases of metabolic syndrome according to the American Heart Association (AHA) and the National Heart, Lung, and Blood Institute (NHLBI) definition[16] in young adulthood was low ($n = 17$). The z-score was based on the AHA/NHLBI definition with additional inclusion of fasting insulin. Thus, WC, the mean of diastolic and systolic BP, triglycerides, HDL (inverted), fasting glucose, and fasting insulin were standardized and subsequently summed to create a continuous metabolic syndrome z-score. Standardization in young adulthood (follow up) was done according to the baseline distribution (mean ± SD) of each risk factor.

Statistics

Associations of screen time use in adolescence with cardiovascular risk factors in young adulthood were analysed using multiple linear regression with baseline levels of respective risk factors included as a covariate. In multivariable analyses, we adjusted for parental educational level, current smoking, family history of CVD, frequency of intake of soft drinks, intake of fruit and vegetables, and MVPA. Because we observed no gender- or cohort-dependent associations for any outcomes we present all analysis for men, women, and follow-up time (cohort) combined. Standard linear regression diagnostics were performed, including examining linearity and normality of residuals. Since we and others previously have shown that the association of prolonged TV viewing with metabolic risk may be mediated by adiposity,[14,17] we also analysed the association of screen-viewing time with metabolic syndrome z-score without adiposity included but with adjustment for WC in adolescence. Furthermore, we included both computer use and TV viewing in the same model to examine the independent role of each type of behaviour. The association of adolescence TV viewing with each outcome was also analysed with additional adjustment for eating while viewing TV and with adjustment for percentage time spent on sedentary behaviour. Because adiposity also have been shown to predict sedentary time,[18] we also analysed if BMI and WC in adolescence was associated with screen-viewing time in young adulthood.

We then examined the association of change in viewing time with each respective cardiovascular risk factor in young adulthood. We used the difference in young adult and adolescence viewing time as a continuous variable adjusting for adolescence viewing time, and we also analysed change in TV viewing and total screen time as categorical variables using the following categories: stable or decrease (≤0 hours/day), modest increase (>0–2 hours/day), and large increase (>2 hours/day). A test for linear trend across groups of change in the categorical analysis was done by treating the 'change variable' as ordinal in the models.

As information on accelerometry measured MVPA and sedentary behaviour at baseline was missing among 161 individuals (37%), we imputed missing values using a multiple univariate linear regression imputation approach ('mi impute' in STATA) including all covariates. Beta coefficients and SEs were obtained based on 20 imputed datasets while the variability between imputations is adjusted for.[19] We did not observe appreciable differences in magnitude of effect estimates from complete case analyses compared with analyses on imputed dataset, although the CI's were wider in complete case analyses.

All statistical analyses were performed in STATA 11.2 with alpha = 0.05 (two-sided). As the study is observational and the nature of the present analysis is exploratory rather than a confirmatory analysis of a clinical trial, no adjustments for multiple testing were carried out.

Results

The characteristics of individuals with baseline measurements that were lost to follow up ($n = 351$) are shown in the supplementary table. TV viewing time, SBP, glucose, and intake of soft drinks was higher and a larger proportion was from parents with only a basic education among individuals lost to follow up or with missing data. Table 1 shows the baseline characteristics of the study population by levels of TV viewing in adolescence. TV viewing at baseline was correlated with glucose, insulin, metabolic syndrome z-score, intake of soft drinks, and intake of fruit and vegetables ($p < 0.05$). There was also a tendency that

Table 1. Baseline characteristics by television viewing time in adolescence

	Television viewing time in adolescence (hours/day)			
	0–1 ($n = 163$)	1–3 ($n = 224$)	>3 ($n = 48$)	p-value
Age (years)	15.6 ± 0.4	15.6 ± 0.4	15.6 ± 0.4	0.64
Gender (boys)	41.7	45.1	60.4	0.07
Body mass index (kg/m^2)	21.0 ± 2.4	20.8 ± 2.4	21.4 ± 3.5	0.25
Waist circumference (cm)	71.7 ± 6.1	71.3 ± 6.4	73.6 ± 8.8	0.08
Systolic BP (mmHg)	109.2 ± 9.8	110.4 ± 10.1	111.5 ± 9.6	0.28
Diastolic BP (mmHg)	61.8 ± 6.2	61.9 ± 6.5	61.1 ± 6.9	0.71
Triglyceride (mmol/l)	0.9 ± 0.4	0.9 ± 0.4	1.0 ± 0.7	0.42
HDL-C (mmol/l)	1.4 ± 0.3	1.4 ± 0.3	1.3 ± 0.3	0.09
Glucose (mmol/l)	5.0 ± 0.4	5.1 ± 0.4	5.2 ± 0.4	<0.01
Insulin (pmol/l)	64.3 ± 29.1	69.9 ± 35.4	79.0 ± 42.5	0.03
Metabolic syndrome z-score	−0.2 ± 2.6	−0.1 ± 2.5	1.2 ± 3.5	<0.01
Computer use (hours/day)	0.7 ± 0.8	0.6 ± 0.7	0.8 ± 0.9	0.21
Soft drinks (servings/month)	7.9 ± 7.9	9.7 ± 9.0	11.9 ± 9.9	0.01
Fruits and vegetables (servings/month)	41.0 ± 16.4	37.0 ± 17.9	31.4 ± 15.3	<0.01
MVPA (% of total time)	5.9 ± 3.0	5.6 ± 3.0	6.1 ± 4.6	0.72
Sedentary (% of total time)	58.3 ± 8.8	57.9 ± 8.2	55.5 ± 12.0	0.38
Parental education level (1/2/3)	9.8/23.3/66.9	10.3/30.8/58.9	10.4/31.3/58.3	0.53
Family history of CVD	26.4	30.8	31.3	0.60

Values are mean ± SD or %; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; MVPA, moderate and vigorous physical activity level.

prolonged TV viewing was correlated with higher WC and lower HDL and to be higher among boys compared to girls ($p < 0.10$) at baseline.

TV viewing, computer use, and total screen time increased noticeably from 1.6 hours/day of TV viewing, 0.6 hours/day of computer use, and 2.2 hours/day of total screen time in adolescence to 3.2 hours/day of TV viewing, 2.9 hours/day of computer use, and 6.1 hours/day of total screen time in young adulthood (Figure 1). Changes were fairly similar in men and women and between cohorts ($p > 0.1$ for interaction). TV viewing, computer use, and total screen time tracked with stability coefficients (partial correlation coefficients) of 0.36 (95% CI 0.27 to 0.45), 0.15 (95% CI 0.05 to 0.25), and 0.30 (95% CI 0.20 to 0.39) from adolescence to young adulthood (age-, gender-, and cohort-adjusted) indicating moderate tracking of TV viewing and total screen time and low tracking of computer use.

Table 2 shows the association of TV viewing, computer use, and total screen time in adolescence with cardiovascular risk factors in young adulthood. In multivariable-adjusted models, for each 1-hour increment in TV viewing time in adolescence, the levels of respective outcomes in young adulthood increased by 0.24 (95% CI 0.00 to 0.49) kg/m^2 BMI, 0.83 (95% CI 0.13 to 1.53) cm WC, 0.05 (95% CI 0.01 to 1.10) mmol/l triglycerides, 2.00 (95% CI −0.19 to 4.17) pmol/l insulin, and 0.45 (95% CI 0.14 to 0.76) SD metabolic syndrome z-score. Slightly weaker associations were observed for total screen time with the outcomes. In multivariable-adjusted analyses, total screen time was significantly associated with BMI, WC, triglycerides, and metabolic syndrome z-score. Additional adjustment for TV viewing or total screen time in adulthood attenuated the associations of adolescence viewing time with all risk factors, except for triglyceride which remained significant for both exposures. However, associations with WC and metabolic syndrome z-score were marginally significant for both adolescence TV viewing and total screen time after adjustment for adult viewing time ($p < 0.1$). Additional adjustment for eating while viewing TV or objectively measured sedentary time did not materially change the results. Excluding adiposity from the metabolic syndrome z-score and adjusting for WC in adolescence slightly attenuated the associations with TV viewing or total screen time, notwithstanding they were still significantly associated with metabolic syndrome z-score ($p < 0.05$). No associations with any outcomes were observed for computer use in adolescence ($p > 0.05$). Including both TV viewing and computer use separately in the same model, TV viewing in adolescence was independently associated with BMI, WC, triglycerides, and metabolic syndrome z-score in

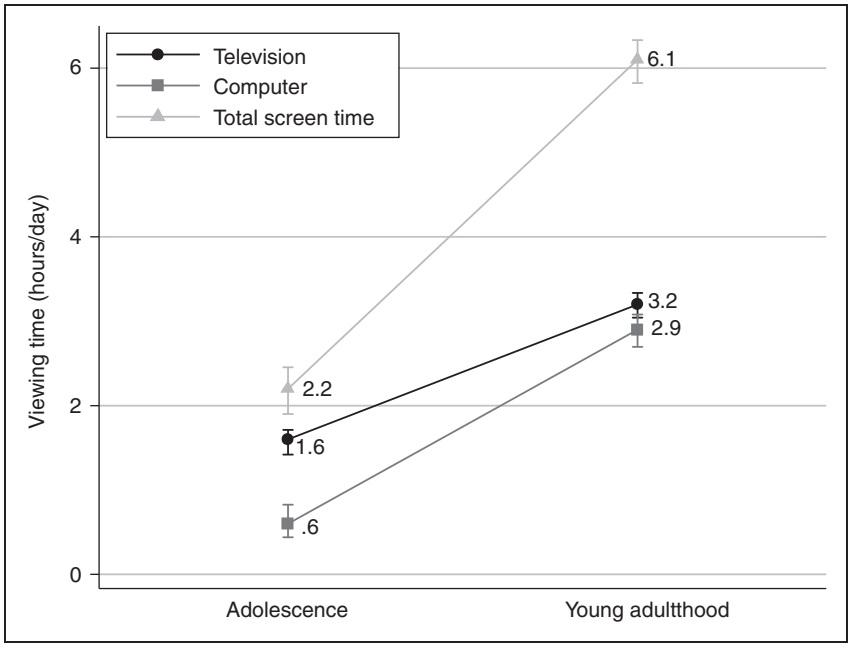

Figure 1. Age-, gender-, and cohort-adjusted estimates (with 95% CI) of TV viewing, computer use, and total screen time during leisure from adolescence to young adulthood ($n = 435$).

young adulthood in multivariable-adjusted analyses. We also explored the possibility of reverse causality (i.e. that adiposity predicts viewing time). Neither BMI nor WC in adolescence predicted any type of screen-viewing time in young adulthood.

In multivariable-adjusted analyses, changes in any type of viewing time from adolescence to young adulthood were consistently positively associated with BMI, insulin, and metabolic syndrome z-score in young adulthood (Table 3). Individuals who increased their TV viewing, computer use, or total screen time with more than 2 hours/day had 0.90 (95% CI 0.12 to 1.69), 0.95 (95% CI 0.01 to 1.88), and 1.40 (95% CI 0.28 to 2.51) kg/m^2 higher BMI respectively in young adulthood compared with individuals who remained stable or decreased their viewing time. Insulin levels were 7.62 (95% CI 0.59 to 14.67), 10.67 (95% CI 2.34 to 19.00), and 8.14 (95% CI −1.80 to 18.08) pmol/l higher among individuals who increased their TV viewing, computer use, or total screen time respectively with more than 2 hours/day compared with individuals who remained stable or decreased their viewing time. Including change in TV viewing and computer use in the same model, changes in both types of viewing were independently associated with BMI and insulin in continuous multivariable-adjusted analyses.

Discussion

In this population-based prospective study, prolonged TV viewing and total screen time in adolescence, and increases in screen time through young adulthood, were consistently associated with greater adiposity and clustered CVD risk in young adulthood. The associations were independent of various confounding factors, including objectively measured MVPA and showed evidence of dose–response relationships. Associations were generally attenuated after adjustment for viewing time in young adulthood, which suggest that prolonged viewers in adolescence are likely to be prolonged viewers in young adulthood as indicated by the moderate stability coefficients of TV viewing and total screen time. Whereas adolescent computer use was not associated with any of the cardiovascular outcomes in young adulthood, increases in computer use during leisure time from adolescence to young adulthood was associated with higher levels of BMI and insulin in young adulthood independent of changes in TV viewing. Collectively, these findings provide support for recommending limiting screen-viewing time among youth.

Our findings on TV viewing are consistent with a previous study among New Zealanders followed from childhood to young adulthood; in this study, prolonged TV viewing in childhood and adolescence was associated with greater BMI, lower cardiorespiratory fitness, and raised cholesterol in young adulthood independent of physical activity level.[11] Another study from the USA among 13-year-olds followed over 5 years found that TV viewing was positivity associated with the risk of high systolic BP.[20] We extend these findings by showing that both TV viewing and total screen time in adolescence, and change in TV viewing

Table 2. Television viewing, computer use, and total screen time in adolescence and cardiovascular risk factors in young adulthood

	Time in adolescence	
	Beta (95% CI)	*p*-value
Television		
Body mass index	0.24 (0.00 to 0.49)	0.049
Waist circumference	0.83 (0.13 to 1.53)	0.02
Triglycerides	0.05 (0.01 to 0.10)	0.02
HDL-C	−0.02 (−0.04 to 0.004)	0.12
Systolic BP	0.38 (−0.39 to 1.13)	0.33
Diastolic BP	0.62 (−0.01 to 1.25)	0.06
Glucose	0.02 (−0.01 to 0.06)	0.21
Insulin	2.00 (−0.19 to 4.17)	0.07
Metabolic syndrome z-score	0.45 (0.14 to 0.76)	0.005
Computer		
Body mass index	0.20 (−0.21 to 0.61)	0.33
Waist circumference	0.30 (−0.88 to 1.46)	0.63
Triglycerides	0.02 (−0.05 to 0.10)	0.55
HDL-C	0.01 (−0.03 to 0.05)	0.56
Systolic BP	−0.18 (−1.44 to 1.08)	0.78
Diastolic BP	−0.06 (−1.12 to 1.00)	0.91
Glucose	−0.02 (−0.08 to 0.03)	0.43
Insulin	0.65 (−2.99 to 4.30)	0.73
Metabolic syndrome z-score	0.03 (−0.48 to 0.55)	0.90
Total screen time		
Body mass index	0.24 (0.03 to 0.46)	0.03
Waist circumference	0.71 (0.10 to 1.32)	0.02
Triglycerides	0.05 (0.009 to 0.09)	0.02
HDL-C	−0.01 (−0.03 to 0.009)	0.29
Systolic BP	0.24 (−0.42 to 0.90)	0.47
Diastolic BP	0.45 (−0.10 to 1.01)	0.11
Glucose	0.01 (−0.02 to 0.04)	0.50
Insulin	1.70 (−0.20 to 3.60)	0.08
Metabolic syndrome z-score	0.35 (0.08 to 0.62)	0.01

Models were adjusted for baseline of risk factor, age, gender, cohort, parental education level, current smoking status, moderate and vigorous physical activity, intake of soft drinks, fruit- and vegetable intake, and family history of cardiovascular disease. Beta coefficient (95% CI) represents change in risk factor in young adulthood per each 1 hour/day change in viewing time in adolescence. HDL-C, high-density lipoprotein cholesterol.

and computer use, are independently associated with unfavourable levels of several cardiovascular risk factors in young adulthood.

Because previous studies among children, adolescents, and adults on the associations of objectively measured sedentary behaviour with cardiovascular risk factors have been equivocal[18,21,22] it is unclear if sedentariness *per se* is the principle cause of the harmful cardiovascular effect of prolonged screen-viewing time. It is possible that especially TV viewing are accompanied by other unhealthy lifestyle, such as eating more unhealthy food and increasing or initiating alcohol drinking or smoking during and beyond TV viewing time,[23–25] may exert effects on cardiovascular risk factors beyond what originates from sedentariness. When we adjusted for eating while viewing TV, no change in the estimates was observed; nevertheless, because we observed weaker associations of computer use with cardiovascular risk, it is likely that the influence of prolonged TV viewing at least partly is mediated by these exposures and not only by sedentariness. Possible explanations to why computer use in youth was unrelated to CVD risk factors in young adulthood could be that youth in the present study on average spent little time using a computer, that computer use is less sedentary compared with TV viewing, or that exposure to factors such as food advertisements are more intense for TV viewing compared with computer use. We also found that the association of TV viewing with clustered cardiovascular risk was only partly mediated by adiposity. This is in accordance with studies among adults having incident CVD or type 2 diabetes as outcomes,[3,6] but in opposite to our previous cross-sectional analysis among children and adolescents[14] and a previous study among adults.[26]

Limited amount of evidence from randomized trials on restricting TV viewing or screen-viewing time exists. However, the few studies that have been carried out provide some support of the associations observed here. Two randomized trials among children have shown that reducing TV viewing time can lead to favourable changes in adiposity status.[27,28] Another small-scale randomized trial among overweight or obese adults did not find a statistically significant change in adiposity status from restricting TV viewing time during a period of 3 weeks, but did see an increase in energy expenditure.[29]

There are a number of limitations to this study. All screen time measures were self-reported and measurement errors are therefore inevitable. Loss to follow up and missing data can lead to bias if the associations are different in these individuals. We found differences in some baseline characteristics among individuals lost to follow up or with missing data compared with the individuals with complete data. However, associations between TV viewing and outcomes were fairly similar by parental educational level (data not shown), which gives us some confidence that the associations are unaffected by selection bias. In addition, our study was not adequately powered to consistently do stratified analyses by cohort, which could provide valuable information about the timing of interventions to prevent the large increase in viewing time. Other limitations of this study include the possibility of unknown and residual confounding, although we adjusted for important

Table 3. Change in TV viewing, computer use, and total screen time from adolescence to young adulthood and cardiovascular risk factors in young adulthood

	Stable or decrease (≤0 hours/day)	Modest increase (>0 to 2 hours/day)	Large increase (>2 hours/day)	*p*-value for trend	Continuous (per 1 hour/day of change)	*p*
Television	*n* = 86	*n* = 197	*n* = 152			
Body mass index	Ref	0.24 (−0.50 to 0.98)	0.90 (0.12 to 1.69)	0.01	0.28 (0.13 to 0.43)	<0.001
Waist circumference	Ref	−0.72 (−2.83 to 1.38)	1.25 (−1.01 to 3.50)	0.14	0.58 (0.15 to 1.02)	0.009
Triglycerides	Ref	−0.02 (−0.15 to 0.20)	0.09 (−0.06 to 0.23)	0.15	0.01 (−0.02 to 0.04)	0.37
HDL-C	Ref	0.004 (−0.06 to 0.07)	−0.05 (−0.12 to 0.02)	0.10	−0.01 (−0.03 to 0.002)	0.09
Systolic BP	Ref	1.26 (−1.03 to 3.54)	1.80 (−0.64 to 4.23)	0.16	0.37 (−0.11 to 0.84)	0.13
Diastolic BP	Ref	0.27 (−1.65 to 2.18)	1.21 (−0.85 to 3.26)	0.20	0.25 (−0.15 to 0.65)	0.22
Glucose	Ref	0.05 (−0.05 to 0.15)	0.04 (−0.07 to 0.15)	0.61	0.01 (−0.01 to 0.03)	0.49
Insulin	Ref	2.41 (−4.17 to 8.99)	7.62 (0.59 to 14.67)	0.02	2.19 (0.82 to 3.55)	0.002
Metabolic syndrome z-score	Ref	0.07 (−0.85 to 1.00)	1.02 (0.03 to 2.01)	0.02	0.27 (0.08 to 0.46)	0.006
Computer	*n* = 50	*n* = 234	*n* = 151			
Body mass index	Ref	0.53 (−0.38 to 1.44)	0.95 (0.01 to 1.88)	0.03	0.10 (0.01 to 0.20)	0.03
Waist circumference	Ref	2.55 (−0.08 to 5.17)	2.87 (0.19 to 5.55)	0.09	0.08 (−0.20 to 0.35)	0.58
Triglycerides	Ref	0.09 (−0.08 to 0.26)	0.10 (−0.08 to 0.27)	0.39	0.005 (−0.01 to 0.02)	0.54
HDL-C	Ref	0.04 (−0.05 to 0.12)	−0.02 (−0.10 to 0.07)	0.23	−0.005 (−0.01 to 0.003)	0.23
Systolic BP	Ref	−0.60 (−3.43 to 2.22)	0.03 (−2.87 to 2.92)	0.73	0.25 (−0.05 to 0.56)	0.10
Diastolic BP	Ref	−0.23 (−2.61 to 2.15)	0.52 (−1.92 to 2.95)	0.46	0.30 (0.05 to 0.55)	0.02
Glucose	Ref	−0.07 (−0.19 to 0.06)	−0.04 (−0.17 to 0.09)	0.94	0.001 (−0.01 to 0.01)	0.92
Insulin	Ref	7.72 (−0.42 to 15.87)	10.67 (2.34 to 19.00)	0.02	1.07 (0.22 to 1.92)	0.01
Metabolic syndrome z-score	Ref	0.61 (−0.55 to 1.77)	1.09 (−0.10 to 2.28)	0.06	0.12 (−0.002 to 0.24)	0.05
Total screen time	*n* = 29	*n* = 114	*n* = 292			
Body mass index	Ref	0.96 (−0.22 to 2.15)	1.40 (0.28 to 2.51)	0.01	0.14 (0.06 to 0.21)	0.001
Waist circumference	Ref	3.04 (−0.35 to 6.43)	3.75 (0.56 to 6.94)	0.04	0.18 (−0.04 to 0.41)	0.10
Triglycerides	Ref	0.09 (−0.13 to 0.30)	0.20 (−0.007 to 0.40)	0.01	0.006 (−0.008 to 0.02)	0.41
HDL-C	Ref	−0.007 (−0.11 to 0.10)	−0.03 (−0.13 to 0.07)	0.32	−0.006 (−0.01 to 0.007)	0.08
Systolic BP	Ref	4.61 (0.95 to 8.27)	4.66 (1.21 to 8.10)	0.06	0.26 (0.02 to 0.50)	0.04
Diastolic BP	Ref	2.43 (−0.64 to 5.51)	3.60 (0.79 to 6.49)	0.01	0.25 (0.05 to 0.45)	0.01
Glucose	Ref	−0.03 (−0.20 to 0.13)	0.03 (0.13 to 0.18)	0.30	0.002 (−0.009 to 0.01)	0.68
Insulin	Ref	0.78 (−9.79 to 11.34)	8.14 (−1.80 to 18.08)	0.006	1.23 (0.54 to 0.92)	<0.001
Metabolic syndrome z-score	Ref	1.05 (−0.44 to 2.54)	1.92 (0.52 to 3.33)	0.001	0.14 (0.04 to 0.24)	0.005

Estimates are beta coefficients (95% CI) from multivariable models adjusted for baseline levels of risk factor and viewing time, age, gender, cohort, parental education level, current smoking status, moderate and vigorous physical activity, current smoking status, intake of soft drinks, fruit- and vegetable intake, and family history of cardiovascular disease. HDL-C, high-density lipoprotein cholesterol.

confounding factors including objectively measured MVPA. Because the magnitudes of the multivariable-adjusted estimates were substantial for many of the outcomes, it is unlikely that residual or unknown confounding fully accounts for these associations. Finally, some of the statistically significant findings may arise from multiple testing since we tested several CVD risk factors.

In conclusion, our findings suggest that prolonged TV viewing and total screen-viewing time during leisure time in adolescence, and increases in these behaviours, are associated with unfavourable levels of several cardiovascular risk factors in young adulthood. These findings indicate that efforts to reduce these viewing behaviours in youth would be important to prevent adverse cardiovascular effects in adulthood, and provide support for recommending limits in TV viewing and total screen-viewing time among youth.

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Conflict of interest

None declared.

References

1. Currie C, Roberts C, Morgan A, et al. *Young people's health in context. Health Behaviour in School-Aged Children (HBSC) study: international report from the 2001/2002 survey*. World Health Organization: Geneva, 2004, Health Policy for Children and Adolescents, no. 4.
2. Office for Official Publications of the European Community. *Time use at different stages of life. Results from 13 European countries*. Luxembourg: Office for Official Publications, 2003.
3. Grøntved A and Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality. *JAMA* 2011; 305(23): 2448–2455.
4. Stamatakis E, Hamer M and Dunstan DW. Screen-based entertainment time, all-cause mortality, and cardiovascular events: population-based study with ongoing mortality and hospital events follow-up. *J Am Coll Cardiol* 2011; 57(3): 292–299.
5. Fung TT, Hu FB, Yu J, et al. Leisure-time physical activity, television watching, and plasma biomarkers of obesity and cardiovascular disease risk. *Am J Epidemiol* 2000; 152(12): 1171–1178.
6. Wijndaele K, Brage S, Besson H, et al. Television viewing time independently predicts all-cause and cardiovascular mortality: the EPIC Norfolk Study. *Int J Epidemiol* 2011; 40(1): 150–159.
7. Committee on Public Education. Children, adolescents, and television. *Pediatrics* 2001; 107(2): 423–426.
8. Tremblay MS, LeBlanc AG, Janssen I, et al. Canadian sedentary behaviour guidelines for children and youth. *App Physiol Nutr Metab* 2011; 36(1): 59–64.
9. Australian Government, Department of Health and Ageing. *Australia's physical activity recommendations*. Canberra, Australia: Department of Health and Ageing, 2004.
10. Tremblay M, LeBlanc A, Kho M, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. *Int J Behav Nutr Phys Act* 2011; 8(1): 98.
11. Hancox RJ, Milne BJ and Poulton R. Association between child and adolescent television viewing and adult health: a longitudinal birth cohort study. *Lancet* 2004; 364(9430): 257–262.
12. Chinapaw MJM, Proper KI, Brug J, et al. Relationship between young peoples' sedentary behaviour and biomedical health indicators: a systematic review of prospective studies. *Obes Rev* 2011; 12(7): e621–e632.
13. Riddoch C, Edwards D, Page A, et al. The European Youth Heart Study – cardiovascular disease risk factors in children: rationale, aims, design and validation of methods. *J Phys Act Health* 2005; 2: 115–129.
14. Ekelund U, Brage S, Froberg K, et al. TV viewing and physical activity are independently associated with metabolic risk in children: the European Youth Heart Study. *PLoS Med* 2006; 3(12): e488.
15. Kristensen P, Moeller N, Korsholm L, et al. The association between aerobic fitness and physical activity in children and adolescents: the European youth heart study. *Eur J Appl Physiol* 2010; 110(2): 267–275.
16. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. *Circulation* 2005; 112(17): 2735–2752.
17. Stamatakis E and Hamer M. The extent to which adiposity markers explain the association between sedentary behavior and cardiometabolic risk factors. *Obesity* 2012; 20(1): 229–232.
18. Ekelund U, Luan Ja, Sherar LB, et al. Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *JAMA* 2012; 307(7): 704–712.
19. Rubin DB. Multiple imputation after 18+ years. *J Am Stat Ass* 1996; 91(434): 473–489.
20. Dasgupta K, O'Loughlin J, Chen S, et al. Emergence of sex differences in prevalence of high systolic blood pressure. *Circulation* 2006; 114(24): 2663–2670.
21. Healy GN, Matthews CE, Dunstan DW, et al. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003–06. *Eur Heart J* 2011; 32(5): 590–597.
22. Carson V and Janssen I. Volume, patterns, and types of sedentary behavior and cardio-metabolic health in children and adolescents: a cross-sectional study. *BMC Public Health* 2011; 11(1): 274.
23. Wellman RJ, Sugarman DB, DiFranza JR, et al. The extent to which tobacco marketing and tobacco use in films contribute to children's use of tobacco: a meta-analysis. *Arch Pediatr Adolesc Med* 2006; 160(12): 1285–1296.
24. Anderson P, de Bruijn A, Angus K, et al. Impact of alcohol advertising and media exposure on adolescent alcohol use: a systematic review of longitudinal studies. *Alcohol Alcohol* 2009; 44(3): 229–243.
25. Wiecha JL, Peterson KE, Ludwig DS, et al. When children eat what they watch: impact of television viewing on dietary intake in youth. *Arch Pediatr Adolesc Med* 2006; 160(4): 436–442.
26. Stamatakis E, Hamer M and Mishra G. Early adulthood television viewing and cardiometabolic risk profiles in early middle age: results from a population, prospective cohort study. *Diabetologia* 2012; 55(2): 311–320.
27. Robinson TN. Reducing children's television viewing to prevent obesity. *JAMA* 1999; 282(16): 1561–1567.
28. Epstein LH, Roemmich JN, Robinson JL, et al. A randomized trial of the effects of reducing television viewing and computer use on body mass index in young children. *Arch Pediatr Adolesc Med* 2008; 162(3): 239–245.
29. Otten JJ, Jones KE, Littenberg B, et al. Effects of television viewing reduction on energy intake and expenditure in overweight and obese adults: a randomized controlled trial. *Arch Int Med* 2009; 169(22): 2109–2115.

Supplementary Table. Baseline characteristics among individuals lost to follow-up or with missing data and individuals with complete data.

	Lost to follow-up or missing data (n=351)	Complete data (n=435)	P
Age (years)	15.6 (0.4)	15.6 (0.4)	0.82
Gender (% boys)	47.3	45.5	0.62
BMI (kg/m^2)	21.2 (3.1)	20.9 (2.6)	0.12
Waist circumference (cm)	72.6 (7.9)	71.7 (6.6)	0.08
Systolic BP (mmHg)	111.6 (10.7)	110.1 (10.0)	0.04
Diastolic BP (mmHg)	62.7 (6.1)	61.8 (6.4)	0.06
Triglyceride (mmol/l)	0.92 (0.43)	0.91 (0.45)	0.60
HDL-C (mmol/l)	1.39 (0.30)	1.39 (0.33)	0.89
Glucose (mmol/l)	5.15 (0.47)	5.07 (0.42)	0.01
Insulin (pmol/l)	73.5 (39.6)	68.8 (34.3)	0.08
TV viewing (hours/day)	1.8 (1.1)	1.6 (1.1)	0.005
Computer use (hours/day)	0.6 (0.7)	0.6 (0.8)	0.21
Soft drinks (servings/month)	11.3 (9.5)	9.3 (8.7)	0.002
Fruits and vegetables (servings/month)	37.4 (17.7)	37.9 (17.3)	0.69
Parental education level (% 1 / 2 / 3)*	14.8 / 33.1 / 52.1	10.1 / 28.1 / 61.8	0.02
Family history of CVD (%)	28.7	29.2	0.88

Data are means (SD) or numbers (%).

*Based on educational level (International Standard Classification of Education (ISCED) (UNESCO 1997). The ISCED level 1 and 2 were grouped, 3 and 4 were grouped, and 5, 6 and 7 were grouped.

Paper III

Grøntved A, Rimm EB, Willett WC, Andersen LB, Hu FB. A Prospective Study of Weight Training and Risk of Type 2 Diabetes in Men. *Archives of Internal Medicine*. 2012;172(17):1306-12

A Prospective Study of Weight Training and Risk of Type 2 Diabetes Mellitus in Men

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Background: The role of weight training in the primary prevention of type 2 diabetes mellitus (T2DM) is largely unknown.

Methods: To examine the association of weight training with risk of T2DM in US men and to assess the influence of combining weight training and aerobic exercise, we performed a prospective cohort study of 32 002 men from the Health Professionals Follow-up Study observed from 1990 to 2008. Weekly time spent on weight training and aerobic exercise (including brisk walking, jogging, running, bicycling, swimming, tennis, squash, and calisthenics/rowing) was obtained from questionnaires at baseline and biennially during follow-up.

Results: During 508 332 person-years of follow-up (18 years), we documented 2278 new cases of T2DM. In multivariable-adjusted models, we observed a dose-response relationship between an increasing amount of time spent on weight training or aerobic exercise and lower risk of T2DM ($P<.001$ for trend). Engaging in weight training or aerobic exercise for at least 150 minutes per week was independently associated with a lower risk of T2DM of 34% (95% CI, 7%-54%) and 52% (95% CI, 45%-58%), respectively. Men who engaged in aerobic exercise and weight training for at least 150 minutes per week had the greatest reduction in T2DM risk (59%; 95% CI, 39%-73%).

Conclusions: Weight training was associated with a significantly lower risk of T2DM, independent of aerobic exercise. Combined weight training and aerobic exercise conferred a greater benefit.

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REGULAR PHYSICAL ACTIVITY (PA) is a cornerstone in the prevention and management of type 2 diabetes mellitus (T2DM). Achieving a daily amount of moderate or vigorous PA of at least 30 minutes per day is associated with a substantial reduction in the risk of T2DM.[1-4] This is broadly consistent with the current recommendations regarding PA in adults.[5] More recently, evidence from randomized controlled trials[6] has shown that resistance training can improve glycemic control in patients with T2DM, even in the absence of aerobic training. This has led to the recommendation for resistance training 3 times per week in individuals with T2DM.[7,8] However, whereas the evidence that regular aerobic exercise can prevent T2DM is compelling, to our knowledge, no studies have examined the role of weight training in the primary prevention of T2DM.

See also pages 1283 and 1285

In this study, we examined the association of weight training with the risk of T2DM in men observed biennially for 18 years in the Health Professionals Follow-up Study (HPFS). In particular, we examined whether the influence of weight training is independent of aerobic exercise and assessed the combined influence of weight training and aerobic exercise on T2DM risk.

METHODS

STUDY POPULATION

The HPFS is an ongoing prospective cohort study of 51 529 male health professionals aged 40 to 75 years at baseline in 1986. Every 2 years, the cohort participants are sent a questionnaire about diseases and personal and lifestyle characteristics, such as height, weight,

smoking status, dietary intake (food frequency questionnaire), and PA. Ninety-four percent of the cohort has completed at least 1 follow-up questionnaire. For this analysis, we excluded men who reported a history of diabetes, cancer, myocardial infarction, angina, coronary artery bypass graft, other heart conditions, stroke, or pulmonary embolism on the baseline questionnaire (1986), in 1988, and in 1990, leaving a study population of 32 002 participants with information on exposures and covariates. This study was approved by the Harvard School of Public Health institutional review board.

ASSESSMENT OF WEIGHT TRAINING, OTHER PA, AND TELEVISION VIEWING

From 1990 and onward, participants reported their average weekly amount of weight training, other PA, and television viewing biennially. Other PAs included walking, jogging, running, bicycling, swimming, tennis, squash, calisthenics/rowing, and heavy outdoor work. There were 13 response categories ranging from none to greater than 40 hours per week for weight training and other PAs. Participants were also asked about the daily number of flights of stairs climbed and usual walking pace. Of these other PAs, brisk walking, jogging, running, bicycling, swimming, tennis, squash, and calisthenics/rowing were considered aerobic exercises of at least moderate intensity (≥3 metabolic equivalent tasks). We used these activities because they are often performed repetitively and produce dynamic contractions of large muscle groups for an extended period.[5] We calculated the total time spent on aerobic exercise of at least moderate intensity (≥3 metabolic equivalent tasks) and grouped participants into 4 categories: 0, 1 to 59, 60 to 149, and at least 150 minutes per week. We grouped participants in the same categories for weight training. We also constructed a variable representing unstructured PA of at least moderate intensity consisting of metabolic equivalent task–hours per week of heavy outdoor work and stair climbing, as previously described.[9,10] The reproducibility and validity of the PA questionnaire have been assessed in a subsample of the HPFS participants. The Pearson correlation between PA of vigorous intensity from diaries for 4 weeks across different seasons and from the questionnaire was 0.58.[11] For weight training, the correlation was 0.79.[11] Reproducibility from 2 questionnaires was 0.52 for vigorous PAs and 0.50 for weight training. Another study[12] reported a correlation of 0.54 between PA score obtained from a similar questionnaire and maximum oxygen uptake.

ASSESSMENT OF T2DM AND DEATH

We ascertained T2DM that occurred between return of the questionnaire in 1990 and January 31, 2008. Men who reported a diagnosis of T2DM in the biennial follow-up questionnaires were sent a supplementary questionnaire to confirm the diagnosis and obtain information on symptoms, treatment, and diagnostic test results. Between 1990 and 1996, the criteria from the National Diabetes Data Group were used to confirm self-reported diagnosis of T2DM, and from 1998 onward we used the American Diabetes Association criteria. Ninety-seven percent of self-reported T2DM cases (57 of 59) were confirmed by means of medical record review in a validation study in a subgroup of HPFS participants.[10] We identified deaths by searching the National Death Index, from next of kin, or from postal authorities. Death due to cardiovascular disease was classified using the *International Classification of Diseases, Eighth Revision*. The National Death Index has an estimated sensitivity of at least 98%.[13]

ASSESSMENT OF COVARIATES

Family history of T2DM was assessed at baseline by self-report. Smoking status and body mass index (calculated as weight in kilograms divided by height in meters squared) were assessed at baseline and biannually thereafter. Dietary factors were assessed in 1990, 1994, 1998, 2002, and 2006 using a 131-item validated food frequency questionnaire.[14] Daily intake of total energy (calories per day), saturated fat to polyunsaturated fat ratio, trans fat (percentage of total energy), alcohol intake, coffee intake, cereal fiber (grams per day), whole grains (grams per day), and glycemic load were considered covariates in the analyses. We also calculated a dietary index composed of polyunsaturated fat to saturated fat ratio, trans fat (inverted), cereal fiber, whole grains, and glycemic load (inverted) by standardizing and summarizing the respective continuously scaled dietary variables.[15]

STATISTICAL ANALYSIS

Person-time at risk was calculated from the return of the 1990 questionnaire (until January 31, 2008), death, or loss to follow-up, whichever occurred first. Relative risks (RRs) of T2DM by categories of weight training and aerobic exercise were estimated using time-dependent Cox proportional hazards regression. To control for calendar time and age, the analyses were stratified jointly by age (in months) at the start of follow-up and the year of questionnaire return. We calculated cumulative averages of weight training and aerobic PA from baseline (1990) to censoring time to minimize measurement error and to characterize long-term exposure status. In multivariable analysis, we additionally adjusted for aerobic exercise, other PA, television viewing, alcohol intake, coffee intake, smoking, ethnicity, family history of diabetes, and the dietary variables total calorie intake, saturated fat to polyunsaturated fat ratio, trans fat, cereal fiber, whole grains, and glycemic load. Tests for trend were performed by assigning the median value of each category of the exposure and treating this variable as continuous. To examine the combined association of weight training and aerobic exercise, we constructed a joint variable of weight training (4 categories) and aerobic exercise (2 categories representing adherence to current recommendations) and associated that with T2DM risk. A test for multiplicative interaction was performed using the likelihood ratio test by comparing models with main effects and interaction terms and models containing only main effects. We did not see indications that the proportional hazard assumption was violated based on the interaction test between follow-up time and weight training.

We also examined the nature of the possible dose-response relationship between weight training and T2DM by using restricted cubic spline regression with 4 knots.[16] Deviation from linearity was tested using the likelihood ratio test by comparing models with cubic spline terms and models containing only the linear term.

We performed several sensitivity analyses to assess the robustness of the results. First, we used the simple update and the baseline information, respectively, on weight training as an alternative to the cumulative average. Second, we performed an analysis using a 4-year lag in exposure classification to assess the possibility of reverse causality. Third, we included confounding variables assessed on the continuous scale in this form in the models to address the possibility of residual confounding. Fourth, we repeated the analysis with death from all causes treated as a competing risk according to the method of Fine and Gray.[17] All the analyses were conducted using a commercially available software package (SAS, version 9.2; SAS Institute, Inc).

Table 1. Age-Adjusted Baseline (1990) Characteristics of the Study Population by Level of Weight Training per Week[a]

Variable	Weight Training, min/wk			
	0	1-59	60-149	≥150
Participants, No.	26 439	2068	2078	1417
BMI, mean (SD)	25.6 (3.3)	25.1 (2.7)	24.9 (2.6)	24.9 (2.7)
Aerobic exercise, mean (SD), h/wk[b]	3.2 (5.1)	4.4 (5.1)	5.5 (5.4)	6.9 (14.2)
Other physical activity, mean (SD), MET-h/wk[c]	9.1 (22.3)	5.5 (13.5)	6.1 (14.6)	8.4 (16.8)
Television viewing, mean (SD), h/wk	10.3 (8.4)	9.4 (8.0)	9.5 (7.7)	9.6 (7.7)
Alcohol intake, mean (SD), g/d	10.2 (14.5)	10.6 (14.1)	10.8 (13.1)	9.8 (12.5)
Coffee intake, mean (SD), cups/d	1.3 (1.6)	1.1 (1.5)	1.2 (1.6)	1.1 (1.5)
P:S ratio, mean (SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.7 (0.2)
Trans fat, mean (SD), % of total energy	1.5 (0.6)	1.4 (0.6)	1.4 (0.6)	1.3 (0.6)
Cereal fiber, mean (SD), g/d	6.3 (4.3)	7.1 (4.6)	7.1 (4.7)	7.2 (5.0)
Whole grains, mean (SD), g/d	24.6 (20.3)	28.9 (22.7)	29.2 (21.6)	31.8 (29.2)
Glycemic load, mean (SD)	125 (47)	130 (48)	129 (47)	132 (49)
Total energy intake, mean (SD), kcal/d	1928 (600)	1943 (602)	1937 (596)	1942 (598)
Dietary index *z* score, mean (SD)[d]	−0.1 (2.5)	0.5 (2.6)	0.7 (2.6)	0.9 (3.0)
Current smoking, %	8	4	4	5
White race, %	96	94	97	96
Family history of diabetes, %	15	15	15	14

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET, metabolic equivalent task; P:S ratio, polyunsaturated fat to saturated fat ratio.

[a] Values are standardized to the age distribution of the study population.

[b] Aerobic exercise consists of walking at a brisk pace, jogging, running, bicycling, swimming, tennis, squash, and calisthenics/rowing.

[c] Other physical activity consists of heavy outdoor work and stair climbing.

[d] Dietary index is the sum of standardized P:S ratio, trans fat (inverted), cereal fiber, whole grains, and glycemic load (inverted).

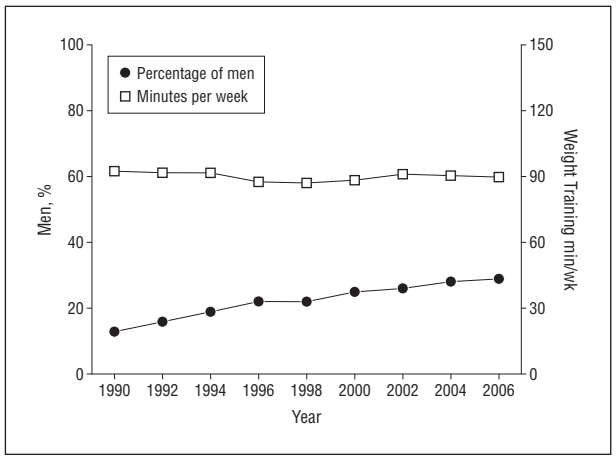

Figure 1. Participation in weight training over time (1990-2006). Data are the age-adjusted percentage of men engaged in weight training and mean minutes per week of weight training in men engaged in weight training across study year.

RESULTS

During 508 332 person-years of follow-up (18 years), we documented 2278 new cases of T2DM. **Table 1** provides the baseline characteristics of the study population by level of weight training per week. Fourteen percent of men reported weight training at baseline. Whereas the age-adjusted percentage of men who engaged in weight training increased with time to 29% in 2006, the average time spent weight training in these individuals seemed stable over time (**Figure 1**). Men who reported weight training at least 150 minutes per week at baseline performed more aerobic exercise, viewed less television, drank less alcohol, were less likely to smoke, and had a healthier dietary intake profile (except for glycemic load) compared with men reporting no weight training.

Table 2 examines the association of weight training and aerobic exercise with the risk of T2DM. In multivariable-adjusted analysis including aerobic exercise, men performing weight training 1 to 59, 60 to 149, and at least 150 minutes per week had RRs of 0.88, 0.75, and 0.66 for lower risk of T2DM ($P < .001$ for trend), respectively, compared with men reporting no weight training. The RRs of T2DM for men performing 1 to 59, 60 to 149, and at least 150 minutes per week of aerobic exercise compared with men reporting no aerobic exercise were 0.93, 0.69, and 0.48 respectively ($P < .001$ for trend), in multivariable-adjusted analysis. When using the baseline information only or the simple updated information on weight training (instead of the cumulatively updated information), results modestly attenuated (baseline: multivariable-adjusted RR = 0.67; 95% CI, 0.51-0.88; and simple updated: multivariable-adjusted RR = 0.75; 95% CI, 0.60-0.94 for the highest categories of weight training). Using a 4-year lag in exposure classification strengthened the association (multivariable-adjusted RR = 0.50; 95% CI, 0.33-0.76 for the highest category of weight training). To assess the possibility of residual confounding, we included covariates as continuous variables where possible, but this did not materially change the results. To further address the possibility that the association of weight training with risk of T2DM was due to confounding by aerobic exercise, we restricted the analysis to men who reported no aerobic exercise. This analysis showed that any weight training was associated with 48% (95% CI, 1%-72%) lower risk compared with no weight training in multivariable-adjusted analysis. In a secondary analysis, we also analyzed whether weight training was associated with mor-

Table 2. Weight Training, Aerobic Exercise, and Risk of Type 2 Diabetes Mellitus in Men From the Health Professionals Follow-up Study (1990-2008)[a]

Variable	Activity, min/wk				*P* Value for Trend
	0	1-59	60-149	≥150	
Weight training					
Median time, min/wk	0	17	85	193	
No. of cases	1630	507	109	32	
Person-y	322 984	130 190	39 936	15 221	
Age adjusted	1 [Reference]	0.72 (0.65-0.80)	0.53 (0.44-0.65)	0.46 (0.32-0.65)	<.001
Multivariable-adjusted model 1[b]	1 [Reference]	0.78 (0.71-0.87)	0.61 (0.50-0.75)	0.53 (0.37-0.76)	<.001
Multivariable-adjusted model 2[c]	1 [Reference]	0.88 (0.79-0.98)	0.75 (0.61-0.92)	0.66 (0.46-0.93)	<.001
Multivariable-adjusted model 3[d]	1 [Reference]	0.92 (0.82-1.02)	0.82 (0.67-1.00)	0.71 (0.49-1.00)	.009
Aerobic exercise[e]					
Median time, min/wk	0	27	97	360	
No. of cases	395	589	445	849	
Person-y	56 897	85 616	94 942	270 877	
Age adjusted	1 [Reference]	0.93 (0.79-1.03)	0.63 (0.54-0.72)	0.39 (0.35-0.45)	<.001
Multivariable-adjusted model 1[b]	1 [Reference]	0.92 (0.81-1.05)	0.67 (0.58-0.78)	0.46 (0.40-0.52)	<.001
Multivariable-adjusted model 2[c]	1 [Reference]	0.93 (0.81-1.06)	0.69 (0.60-0.80)	0.48 (0.42-0.55)	<.001
Multivariable-adjusted model 3[d]	1 [Reference]	1.00 (0.88-1.15)	0.80 (0.69-0.92)	0.61 (0.53-0.70)	<.001

[a] Data are given as relative risk (95% CI) except where indicated otherwise.
[b] Adjusted for age (months), smoking (never, past, or current with cigarette use of 1-14, 15-24, or ≥25 per day), alcohol consumption (0, 1-5, 6-10, 11-15, or >15 g/d), coffee intake (0, <1, 1-3, >3-5, or >5 cups per day), race (white vs nonwhite), family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, and glycemic load (all dietary factors in quintiles).
[c] Additionally adjusted for aerobic exercise (or weight training if aerobic exercise was the exposure), other physical activity of at least moderate intensity (quintiles), and television viewing (quintiles).
[d] Additionally adjusted for body mass index.
[e] Aerobic exercise consists of walking at a brisk pace, jogging, running, bicycling, swimming, tennis, squash, and calisthenics/rowing.

tality from cardiovascular disease (n = 1901 deaths) and all causes (n = 6251 deaths). The age-adjusted RRs across categories of weight training were 0.76, 0.79, and 0.78 (P = .009 for trend) for cardiovascular disease mortality and 0.75, 0.82, and 0.89 (P = .002 for trend) for all-cause mortality. After multivariable adjustment including aerobic exercise, the corresponding RRs were 0.90, 1.00, and 0.98 (P = .82 for trend) for cardiovascular disease mortality and 0.88, 1.04, and 1.11 (P = .38 for trend) for all-cause mortality. Treating death from all causes as a competing risk gave results similar to those of the standard Cox proportional hazards regression model in the analysis with T2DM as outcome.

Adjusting for body mass index moderately attenuated the associations of weight training (multivariable-adjusted RR = 0.71; 95% CI, 0.49-1.00 for the highest category) and aerobic exercise (multivariable-adjusted RR = 0.61; 95% CI, 0.53-0.70 for the highest category) with T2DM risk. A subsample of the participants also had information about waist circumference in 1987 and 1996 (413 890 person-years and 1850 cases). Using this information to assess mediation by adiposity attenuated the association of weight training and aerobic exercise to a larger extent (weight training RR = 0.76; 95% CI, 0.51-1.14; and aerobic exercise RR = 0.62; 95% CI, 0.53-0.73 for the highest categories), although the trend across categories was still present for both exercise types ($P < .05$ for trend).

Results of the multivariable-adjusted restricted cubic spline regression showed that the risk of T2DM decreased linearly with increasing time spent weight training (P = .59 for the nonlinear response) (**Figure 2**). For each 60 minutes of weight training per week, the risk of T2DM decreased by 13% (95% CI, 6%-19%; $P < .001$). For aerobic exercise, the relationship clearly seemed nonlinear, with the strongest association at the lower level of aerobic exercise ($P < .001$ for the nonlinear response) (eFigure; http://www.archinternmed.com).

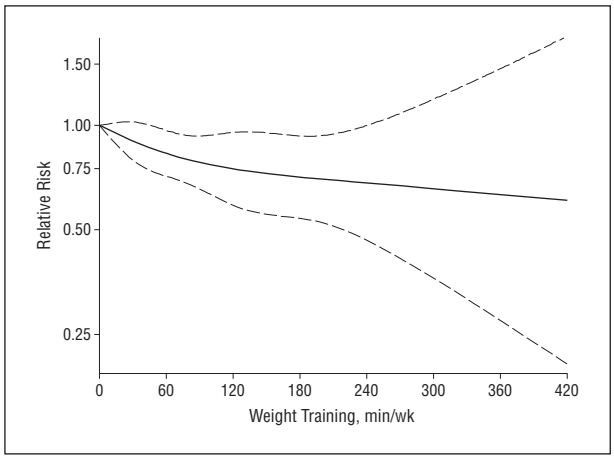

Figure 2. Dose-response relationship between weight training and risk of type 2 diabetes mellitus. Dotted lines represent 95% CIs for the trend obtained from restricted cubic spline regression (4 knots). The model included the following covariates: age (months), aerobic exercise (0, 1-59, 60-149, or ≥150 minutes per week), other physical activity of at least moderate intensity (quintiles), television viewing (quintiles), smoking (never, past, or current with cigarette use of 1-14, 15-24, or ≥25 per day), alcohol consumption (0, 1-5, 6-10, 11-15, or >15 g/d), coffee intake (0, <1, 1-3, >3-5, >5 cups per day), race (white vs nonwhite), family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, and glycemic load (all dietary factors in quintiles). The analysis was truncated to men reporting no more than 420 minutes per week. P = .59 for the nonlinear relationship.

Table 3. Weight Training and Risk of Type 2 Diabetes Mellitus in Men From the Health Professionals Follow-up Study (1990-2008) Stratified by Age, BMI, Family History of Diabetes, and Dietary Index Score[a]

Variable	Weight Training, min/wk				*P* Value for Trend	RR per 60 min/wk	*P* Value of Interaction
	None	1-59	60-149	≥150			
Age, y							
<65 (1125 cases, 289 111 person-y)	1 [Reference]	0.90 (0.77-1.04)	0.64 (0.48-0.85)	0.54 (0.33-0.86)	.002	0.79 (0.69-0.89)	<.001
≥65 (1153 cases, 219 221 person-y)	1 [Reference]	0.87 (0.75-1.01)	0.92 (0.69-1.22)	0.95 (0.56-1.62)	.56	0.96 (0.84-1.10)	
BMI							
<30 (1499 cases, 455 664 person-y)	1 [Reference]	0.87 (0.76-0.99)	0.75 (0.59-0.95)	0.79 (0.53-1.18)	.02	0.90 (0.82-0.98)	.50
≥30 (779 cases, 52 668 person, y)	1 [Reference]	1.00 (0.83-1.21)	0.99 (0.68-1.42)	0.40 (0.18-0.90)	.055	0.87 (0.76-1.00)	
Family history of diabetes mellitus							
Negative (1687 cases, 436 300 person-y)	1 [Reference]	0.88 (0.78-1.00)	0.69 (0.54-0.88)	0.59 (0.38-0.90)	<.001	0.85 (0.78-0.94)	.04
Positive (591 cases, 72 032 person-y)	1 [Reference]	0.86 (0.70-1.07)	0.88 (0.62-1.26)	0.93 (0.49-1.75)	.55	0.92 (0.80-1.06)	
Dietary index score							
<Median (1376 cases, 253 486 person-y)	1 [Reference]	0.91 (0.79-1.04)	0.72 (0.53-0.96)	0.71 (0.43-1.16)	.01	0.89 (0.79-0.99)	.52
>Median (902 cases, 254 847 person-y)	1 [Reference]	0.86 (0.73-1.01)	0.77 (0.58-1.01)	0.62 (0.37-1.19)	.01	0.86 (0.77-0.96)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); RR, relative risk.

[a]Data are given as RR (95% CI). All the models included age (months), smoking (never, past, or current with cigarette use of 1-14, 15-24, or ≥25 per day), alcohol consumption (0, 1-5, 6-10, 11-15, or >15 g/d), coffee intake (0, <1, 1-3, >3-5, >5 cups per day), race (white vs nonwhite), family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, glycemic load (all dietary factors in quintiles), aerobic exercise, other physical activity of at least moderate intensity (quintiles), and television viewing (quintiles).

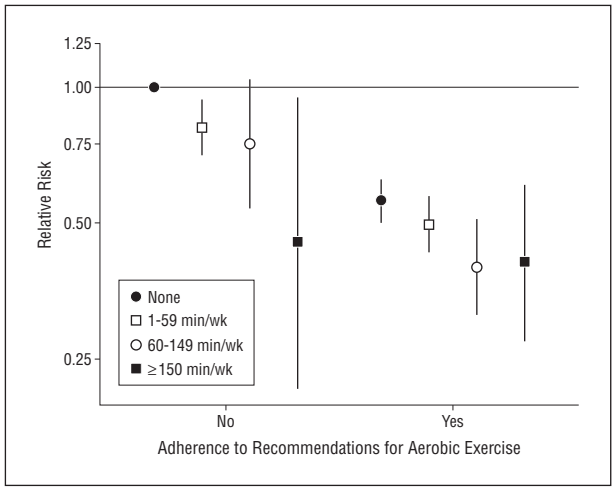

Figure 3. Joint association of weight training and aerobic exercise with the risk of type 2 diabetes mellitus. Data are estimates of relative risk with 95% CIs (vertical line) from multivariable Cox proportional hazards regression models adjusted for age (months), other physical activity of at least moderate intensity (quintiles), television viewing (quintiles), smoking (never, past, or current with cigarette use of 1-14, 15-24, or ≥25 per day), alcohol consumption (0, 1-5, 6-10, 11-15, or >15 g/d), coffee intake (0, <1, 1-3, >3-5, or >5 cups per day), race (white vs nonwhite), family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, whole grain, and glycemic load (all dietary factors in quintiles). Adherence to the recommendations on aerobic exercise is at least 150 minutes per week.

We then examined the association of weight training and aerobic exercise stratified by age (<65 vs ≥65 years), body mass index (<30 vs ≥30), family history of T2DM (yes vs no), and dietary index score (below vs above the median) (**Table 3** and eTable). The association of weight training with T2DM was stronger in men younger than 65 years ($P < .001$ for multiplicative interaction). There was also evidence that the association was stronger in men with no family history of T2DM ($P = .04$ for multiplicative interaction). This was less apparent for aerobic exercise, where associations were fairly similar across these strata (eTable).

Finally, we examined the joint association of weight training and aerobic exercise with the risk of T2DM (**Figure 3**). Men who adhered to the current recommendations on aerobic exercise (≥150 minutes per week) and engaged in weight training of at least 150 minutes per week had the greatest reduction in T2DM risk (RR = 0.41; 95% CI, 0.27-0.61; $P = .26$ for multiplicative interaction).

COMMENT

In this large prospective cohort study with biannual follow-up for 18 years, men who engaged in weight training had a reduced risk of T2DM. The association was independent of aerobic exercise, and even a modest amount of time engaged in weight training seemed to be beneficial. The risk reduction associated with weight training was comparable in magnitude with that of aerobic exercise, with risk reductions of approximately 35% and 50%, respectively, in men performing at least 150 minutes per week of either weight training or aerobic exercise. These results support that weight training serves as an important alternative for individuals who have difficulty adhering to aerobic exercise, but the combination of weight training with aerobic exercise conferred an even greater benefit.

These findings are in agreement with those from a recent meta-analysis[6] of randomized controlled trials showing that resistance training can improve glycemic control in individuals with T2DM. However, no previous studies, to our knowledge, have examined the association of weight training with the risk of T2DM. A variety of cross-sectional studies[18-21] have shown that weight train-

ing, muscle strength, or muscle mass is associated with greater insulin sensitivity or prediabetes. In addition, 2 prospective cohort studies[22,23] have reported that greater muscle strength was associated with a lower risk of incident metabolic syndrome, although association was attenuated with adjustment for aerobic fitness in both studies. Finally, in a study[24] from the HPFS, we reported an inverse association between weight training and risk of coronary heart disease independent of other PAs. Further studies are needed to examine the associations between weight training and other outcomes, including total and cause-specific mortality.

The 2 largest trials[25,26] of resistance training in individuals with T2DM showed that the combination of aerobic exercise and resistance training conferred further benefit for glycemic control in individuals with T2DM than did either type of exercise alone. We observed that combining aerobic exercise and weight training was associated with the largest reduction in the risk of T2DM. Although we observed that the time spent engaged in weight training provided a fairly comparable reduction in risk compared with the time spent in aerobic exercise, it is unclear whether the total energy expenditure plays the same role for the 2 types of exercise. Because the anaerobic energy expenditure contribution during weight training can be substantial, the energy requirements for weight training may be grossly underestimated compared with that of aerobic exercise using metabolic equivalent task values. Furthermore, we did not obtain specific information about the type and intensity of weight training. Thus, it is uncertain whether the altered daily total energy expenditure from engaging in aerobic exercise is comparable with that from weight training in this study.

Although many of the acute and chronic physiologic responses induced by resistance training and aerobic exercise are similar, there are also distinct effects of each exercise type.[27] At the cellular level, engagement in aerobic exercise increases mitochondrial density and oxidative enzyme activity, thereby facilitating improved fatty acid oxidation, whereas resistance training increases the glycolytic capacity and promotes type II muscle fiber abundance and growth, which enhances the capacity of glucose use.[28] In turn, aerobic exercise leads to greater improvements in aerobic fitness, whereas resistance training favors increased lean body mass and muscle strength.[29,30] Beyond improving glycemic control, both exercise types have been shown to reduce adiposity and improve blood pressure and lipid levels.[31-34]

We did not observe a strong attenuation of the association with weight training after additional adjustment for body mass index. This may be attributable to weight training being able to increase lean mass and reduce fat mass without a major change in body weight, as previously indicated in trials in individuals with T2DM.[25,26] However, using waist circumference indicated that part of the beneficial effect of weight training was mediated by abdominal adiposity. In a previous analysis,[35] weight training was associated with a smaller increase in waist circumference over time in men.

We found that the association of weight training with T2DM risk was attenuated in men 65 years and older and in men with a family history of T2DM. The attenuation of association in these subgroups may be attributed to power. An alternative explanation could be that the intensity of weight training is decreased at older ages. However, we do not have data to test this hypothesis. The possible weakened relationship between weight training and T2DM risk in men with a positive family history deserves more attention in future studies.

The strengths of this study include the large sample size, the long follow-up, and the biannual assessment of exposures and most confounders, including important dietary factors. We also showed that associations were robust to a variety of sensitivity analyses, including an analysis using a 4-year lag in exposure classification. Limitations include that the study comprised only men who were working health professionals and mostly of white race. The findings may, therefore, not be generalizable to women and other ethnic or racial groups of men. Furthermore, we did not explore the importance of type and intensity of weight training as we obtained information only on weekly nonspecific weight training. Finally, there is a possibility of residual and unknown confounding. Because we observed risk reduction with any weight training in individuals reporting no aerobic exercise, it is unlikely that the association of weight training can be explained by residual confounding by aerobic exercise.

In conclusion, this prospective cohort study showed that weight training was associated with a reduced risk of T2DM in a dose-response manner independent of aerobic exercise level. The magnitude of risk reduction associated with weight training was close to that with aerobic exercise. These results support that weight training is a valuable alternative for individuals who have difficulty adhering to aerobic exercise, and adding weight training to aerobic exercise seems to give further protection from T2DM. Further research should examine the effect of duration, type, and intensity of weight training on T2DM risk in greater detail.

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REFERENCES

1. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care*. 2007;30(3):744-752.
2. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH. A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA*. 1992;268(1):63-67.
3. Waller K, Kaprio J, Lehtovirta M, Silventoinen K, Koskenvuo M, Kujala UM. Leisure-time physical activity and type 2 diabetes during a 28 year follow-up in twins. *Diabetologia*. 2010;53(12):2531-2537.
4. Meisinger C, Löwel H, Thorand B, Döring A. Leisure time physical activity and the risk of type 2 diabetes in men and women from the general population. The MONICA/KORA Augsburg Cohort Study. *Diabetologia*. 2005;48(1):27-34.
5. Physical Activity Guidelines Advisory Committee. *Physical Activity Guidelines Advisory Committee Report, 2008*. Washington, DC: US Dept of Health and Human Services; 2008.
6. Umpierre D, Ribeiro PAB, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2011;305(17):1790-1799.
7. Colberg SR, Sigal RJ, Fernhall B, et al; American College of Sports Medicine; American Diabetes Association. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes Care*. 2010;33(12):e147-e167.
8. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care*. 2011;34(suppl 1):S11-S61.
9. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc*. 2011;43(8):1575-1581.
10. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med*. 2001;161(12):1542-1548.
11. Chasan-Taber S, Rimm EB, Stampfer MJ, et al. Reproducibility and validity of a self-administered physical activity questionnaire for male health professionals. *Epidemiology*. 1996;7(1):81-86.
12. Jacobs DR Jr, Ainsworth BE, Hartman TJ, Leon AS. A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Med Sci Sports Exerc*. 1993;25(1):81-91.
13. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the National Death Index and Equifax Nationwide Death Search. *Am J Epidemiol*. 1994;140(11):1016-1019.
14. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992;135(10):1114-1136.
15. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001;345(11):790-797.
16. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology*. 1995;6(4):356-365.
17. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
18. Cheng YJ, Gregg EW, De Rekeneire N, et al. Muscle-strengthening activity and its association with insulin sensitivity. *Diabetes Care*. 2007;30(9):2264-2270.
19. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes: findings from the Third National Health and Nutrition Examination Survey. *J Clin Endocrinol Metab*. 2011;96(9):2898-2903.
20. Barzilay JI, Cotsonis GA, Walston J, et al; Health ABC Study. Insulin resistance is associated with decreased quadriceps muscle strength in nondiabetic adults aged >or=70 years. *Diabetes Care*. 2009;32(4):736-738.
21. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. *Med Sci Sports Exerc*. 2009;41(7):1361-1367.
22. Wijndaele K, Duvigneaud N, Matton L, et al. Muscular strength, aerobic fitness, and metabolic syndrome risk in Flemish adults. *Med Sci Sports Exerc*. 2007;39(2):233-240.
23. Jurca R, Lamonte MJ, Barlow CE, Kampert JB, Church TS, Blair SN. Association of muscular strength with incidence of metabolic syndrome in men. *Med Sci Sports Exerc*. 2005;37(11):1849-1855.
24. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA*. 2002;288(16):1994-2000.
25. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A_{1c} levels in patients with type 2 diabetes: a randomized controlled trial. *JAMA*. 2010;304(20):2253-2262.
26. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. *Ann Intern Med*. 2007;147(6):357-369.
27. Hawley JA. Molecular responses to strength and endurance training: are they incompatible? *Appl Physiol Nutr Metab*. 2009;34(3):355-361.
28. LeBrasseur NK, Walsh K, Arany Z. Metabolic benefits of resistance training and fast glycolytic skeletal muscle. *Am J Physiol Endocrinol Metab*. 2011;300(1):E3-E10.
29. Peterson MD, Sen A, Gordon PM. Influence of resistance exercise on lean body mass in aging adults: a meta-analysis. *Med Sci Sports Exerc*. 2011;43(2):249-258.
30. Peterson MD, Rhea MR, Sen A, Gordon PM. Resistance exercise for muscular strength in older adults: a meta-analysis. *Ageing Res Rev*. 2010;9(3):226-237.
31. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: a meta-analysis of randomized controlled trials. *Prev Med*. 2009;48(1):9-19.
32. Kraus WE, Houmard JA, Duscha BD, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *N Engl J Med*. 2002;347(19):1483-1492.
33. Cornelissen VA, Fagard RH. Effect of resistance training on resting blood pressure: a meta-analysis of randomized controlled trials. *J Hypertens*. 2005;23(2):251-259.
34. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2002;136(7):493-503.
35. Koh-Banerjee P, Chu NF, Spiegelman D, et al. Prospective study of the association of changes in dietary intake, physical activity, alcohol consumption, and smoking with 9-y gain in waist circumference among 16 587 US men. *Am J Clin Nutr*. 2003;78(4):719-727.

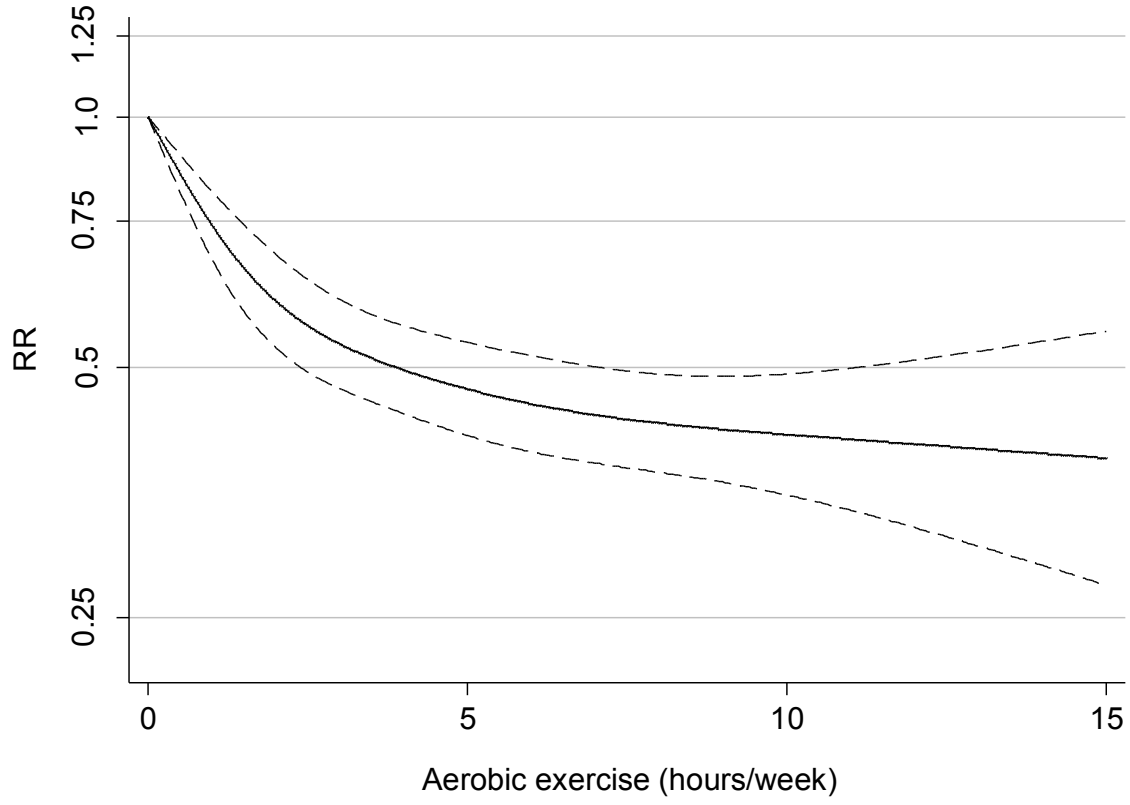
eTable. Aerobic exercise and risk of type 2 diabetes in men from Health Professional Follow-up Study (1990-2008) stratified by age, body mass index, family history of type 2 diabetes, and dietary index score.

	Aerobic Exercise (minutes/week)				
	None	1 – 59	60 – 149	≥150	p trend
Age (years)					
<65 (1,125 cases, 289,111 person years)	1	0.86 (0.72-1.04)	0.56 (0.46-0.69)	0.43 (0.36-0.52)	<0.001
≥65 (1,153 cases, 219,221 person years)	1	0.99 (0.82-1.20)	0.86 (0.70-1.05)	0.54 (0.44-0.65)	<0.001
BMI (kg/m^2)					
<30 (1,499 cases, 455,664 person years)	1	0.95 (0.80-1.13)	0.76 (0.65-0.93)	0.57 (0.48-0.68)	<0.001
≥30 (779 cases, 52,668 person years)	1	1.06 (0.85-1.31)	0.77 (0.61-0.98)	0.59 (0.47-0.75)	<0.001
Family history of type 2 diabetes					
Negative (1,687 cases, 436,300 person years)	1	0.96 (0.82-1.12)	0.68 (0.58-0.81)	0.46 (0.39-0.54)	<0.001
Positive (591 cases, 72,032 person years)	1	0.84 (0.64-1.11)	0.71 (0.53-0.94)	0.55 (0.42-0.73)	<0.001
Dietary index score					
< Median (1,376 cases, 253,486 person years)	1	0.89 (0.75-1.04)	0.68 (0.57-0.81)	0.44 (0.37-0.52)	<0.001
> Median (902 cases, 254,847 person years)	1	1.02 (0.80-1.31)	0.72 (0.56-0.92)	0.55 (0.43-0.69)	<0.001

Data are relative risks (95% CI). All models included age (months), smoking (never, past, or current with cigarette use of 1-14, 15-24, ≥25 per day), alcohol consumption (0, 1-5, 6-10, 11-15, >15 g/d), coffee intake (0, <1, 1-3, 3-5, >5 cups/day), race (white, non-white), family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, wholegrain, glycemic load (all dietary factors in quintiles), weight training, other physical activity of at least moderate intensity (quintiles), and TV viewing (quintiles).

eFigure

Dose reponse relationship between aerobic exercise (hours/week) and risk of type 2 diabetes. Dotted lines are 95% CI for the trend obtained from restriced cubic spline regression (4 knots). The model included the following covariates: age (months), weight training (0, 1-59, 60-149, ≥150 min/week), other physical activity of at least moderate intensity (quintiles), TV viewing (quintiles), smoking (never, past, or current with cigarette use of 1-14, 15-24, ≥25 per day), alcohol consumption (0, 1-5, 6-10, 11-15, >15 g/d), coffee intake (0, <1, 1-3, 3-5, >5 cups/day), race (white, non-white), family history of diabetes, intake of total energy, trans fat, polyunsaturated fat to saturated fat ratio, cereal fiber, wholegrain, and glycemic load (all dietary factors in quintiles) and truncated to men reporting ≤15 hours/week. P<0.001 for a non-linear relationship.



Paper IV

Grøntved A, Ried-Larsen M, Møller NC, Kristensen PL, Froberg K, Brage S, Andersen LB. Muscle strength in youth and cardiovascular risk in young adulthood (The European Youth Heart Study). *British Journal of Sports Medicine.* 2013. (Epub ahead of print).

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Muscle strength in youth and cardiovascular risk in young adulthood (the European Youth Heart Study)

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ABSTRACT

Background Whether muscle strength in youth is related to cardiovascular risk later in life independent of cardiorespiratory fitness is unclear.

Methods We examined the independent association of isometric muscle strength in youth with cardiovascular risk factors in young adulthood using data from the Danish European Youth Heart Study; a population-based prospective cohort study among boys and girls (n=332) followed for up to 12 years. In youth maximal voluntary contractions during isometric back extension and abdominal flexion were determined using a strain-gauge dynamometer and cardiorespiratory fitness was obtained from a maximal cycle ergometer test. Cardiovascular risk factors were obtained in youth and in young adulthood. Associations were examined using multivariable-adjusted regression models including major confounding factors.

Results Each 1 SD difference in isometric muscle strength in youth (0.17 N/kg) was inversely associated with body mass index (BMI; −0.60 kg/m^2, 95% CI −0.97 to −0.22), triglyceride (−0.09 mmol/l, 95% CI −0.16 to −0.02), diastolic blood pressure (BP) (−1.22 mm Hg, 95% CI −2.15 to −0.29) and a composite cardiovascular risk factor score (−0.61 SD, 95% CI −1.03 to −0.20) in young adulthood in multivariable-adjusted analyses including fitness. Associations to triglyceride, diastolic BP and the cardiovascular risk factor score remained with additional adjustment for waist circumference or BMI. Each 1 SD difference in isometric muscle strength in youth was significantly associated with 0.59 (95% CI 0.40 to 0.87) lower odds of general overweight/obesity in young adulthood (p=0.007) and was marginally associated with incident raised BP, raised triglyceride and low high-density lipoprotein cholesterol.

Conclusions This study suggests that greater isometric muscle strength in youth is associated with lower levels of cardiovascular risk factors in young adulthood independent of fitness, adiposity and other confounding factors.

INTRODUCTION

In children and youth low cardiorespiratory fitness is a well-established risk factor for developing cardiovascular disease (CVD) risk factors such as obesity, metabolic syndrome and raised blood pressure (BP).[1 2] While prospective studies have established this in detail;[3] the importance of muscle strength remains less clear. Among adult men, some evidence suggests that low muscle strength is associated with premature mortality independent of cardiorespiratory fitness[4] and engagement in weight training protects against coronary heart disease (CHD)[5] and type 2 diabetes[6] independent of aerobic activity. These epidemiological studies provide support to promote muscle-strengthening activities in addition to aerobic physical activity (PA) for primary prevention in adults. In the current guidelines for PA for children and youth it is recommended that muscle-strengthening activities should be included as part of the 60 min/day of moderate-to-vigorous PA that are endorsed to be largely aerobic.[7 8] Children and adolescents engaging in muscle-strengthening activities can increase their muscular strength,[9] indicating that muscle strength is a marker of participation in muscle-strengthening activities. A recent prospective study based on Swedish male adolescents reported that low muscle strength was inversely associated with premature mortality, although this analysis was not adjusted for cardiorespiratory fitness.[10] We are not aware of prospective studies examining the influence of muscle strength in childhood or youth on CVD risk factors in adulthood independent of cardiorespiratory fitness and other important determinant of CVD risk.

In this study we examined the association of isometric muscle strength in youth with cardiovascular risk factors in young adulthood independent of cardiorespiratory fitness among Danish boys and girls followed up to 12 years in the European Youth Heart Study (EYHS).

METHODS

Design

The current study is based on the Danish cohorts of the EYHS, an ongoing international population-based multicentre study that addresses CVD risk factors in children and adolescents. A detailed description of the sampling procedure of the EYHS is provided elsewhere.[11] In this study, a random sample of 658 15-year-old adolescents were invited to participate in 1997–1998, of whom 429 (65%) agreed to take part in the study. In 2003–2004, another random sample of 771 15-year-old adolescents was invited of whom 444 (58%) agreed to take part. In 2009–2010, a 6-year or 12-year follow-up was conducted where all originally invited participants from 1997–1998 to 2003–2004 were invited again, 281 (43%) and 369 (48%) from the 1997–1998 to 2003–2004 originally invited participated, respectively. Isometric muscle strength was assessed in a subgroup of 243 participants in 1997–1998 (57%) and in 441 (99%) in 2003–2004. The eligible cohort for the current analyses was n=332 individuals who had complete data on all exposure and outcome variables (229 individuals with 6-year follow-up and 103 individuals with 12-year follow-up). Ninety-four per cent of the population at baseline was postpubertal based

on Tanner's stage evaluation performed by trained researchers (pubic hair stages for boys and Tanner's breast development stages for girls) and 93% were white (Caucasian). The local scientific ethics committee approved the study and all participants gave informed consent to participate.

Isometric muscle strength

Isometric muscle strength was obtained during maximal voluntary contraction (MVC) of abdominal and back muscles. The participants were standing upright and positioned with a strap around the shoulders connected to a strain-gauge dynamometer.[12] Assessment of abdominal strength was performed with the back against the dynamometer performing maximal forward flexion. For MVC of the low back muscles, the participants were positioned with the front against the dynamometer performing maximal backward extension. Isometric muscle strength was calculated as the mean of abdominal and back strength (Newton (N)) divided by body weight (N/kg). A previous study among adults have reported high reliability of these particular isometric strength measures (intraclass correlation coefficient >0.9).[13]

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed during a progressive maximal ergometer bicycle test (Ergomedic 839; Monark, Varberg, Sweden) as previously described.[11] Heart rate (HR) was recorded every 5 s throughout the test using a HR monitor (Polar Vantage, Finland). Criteria for a maximal effort were HR of 185 bpm or greater, and a subjective judgement by the observer that the participant could no longer continue, even after encouragement. Maximal power output (wattmax) from the test was used to estimate maximal oxygen uptake using the following equation VO_2-max (ml/min)=0.465+(0.0112×wattmax) +(0.172×sex), where sex is boys=1 and girls=0.[14] VO_2-max was subsequently divided by body weight. The fitness test is highly reproducible (coefficient of variation 2.5–4.8%) and a previous validation study in 15-year-olds have shown that this measure is highly correlated with VO_2-max assessed directly ($r > 0.90$, $p < 0.001$).[15]

Other covariates

Information on watching television (TV) at baseline was obtained using a computer-based questionnaire as described previously.[11] Two questions about the amount of time watching TV (before and after school) were combined to create a summary variable of daily TV watching time (hours/day).[16] Smoking status, monthly frequency soft drinks, fruit and vegetable intake were obtained by self-report in adolescence using the same questionnaire. Family history of CVD (paternal or maternal, yes/no) and parental educational level were obtained by parental self-report. Parental educational status was defined according to the International Standard Classification of Education (ISCED, 1997). However, as the details obtained from the description of education was insufficient, the ISCED seven-point scale was changed to three new groups (1 = basic education; 2 = secondary or postsecondary education and 3 = tertiary education).

Cardiovascular risk factors

Body height, body weight, and waist circumference (WC) were measured using standard anthropometric procedures.[11] Fasting blood samples (overnight) were taken in the morning from the antecubital vein. Samples were aliquoted and separated within 30 min, and then stored at −80°C until they were transported to WHO-certified laboratory in Bristol and Cambridge (UK), for analysis at baseline and in Cambridge (UK) at follow-up. Samples were analysed for serum glucose, high-density lipoprotein cholesterol (HDL-C) and triglyceride. Triglyceride was analysed using the lipase/glycerol kinase/glycerol phosphate oxidase enzymatic method. HDL was analysed using the homogeneous polyanion/cholesterol esterase/oxidase enzymatic method. Glucose was analysed using the hexokinase method. Blood lipids and glucose were measured on an Olympus AU600 autoanalyzer (Olympus Diagnostica, Hamburg, Germany) at baseline and on a Dade Behring Dimension RxL autonalyzer (Siemens Healthcare, Camberley, UK) at follow-up. Between-laboratory correlations in lipids, and glucose for 30 randomly selected samples analysed at both laboratories were 0.94–0.98 at baseline.[17]

Resting BP was measured with a Dinamap paediatric and adult neonatal vital signs monitor (model XL, Critikron, Inc, Tampa, Florida, USA) using an appropriate cuff size (evaluated via arm circumference). After 5 min of seated rest, five measurements were taken at 2 min intervals with the mean of the final three measurements used in all analyses.

We calculated a continuous composite CVD risk z-score using components of the metabolic syndrome suggested by the American Heart Association (AHA) and the National Heart, Lung and Blood Institute (NHLBI).[18] Thus, WC, the mean of diastolic and systolic BP, triglycerides, HDL (inverted) and fasting glucose were standardised and subsequently summed to create a continuous z-score.[19] Standardisation in young adulthood (follow-up) was carried out according to the baseline distribution (mean and SD) of each risk factor.

Abdominal obesity, raised BP, raised triglycerides, low HDL and raised fasting plasma glucose were defined according to Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).[20]

Statistics

We examined the associations of isometric muscle strength in adolescence with cardiovascular risk factors in young adulthood using multiple linear regression with baseline levels of respective risk factors included as a covariate. First, we adjusted models for age at baseline, follow-up time, sex and recruitment period. We then ran multivariable analyses adjusting for baseline information on TV watching, parental educational level, smoking, family history of CVD, frequency of intake of soft drinks and intake of fruit and vegetables. Furthermore, we additionally adjusted for cardiorespiratory fitness and body mass index (BMI) or WC. Standard linear regression diagnostics, including examining linearity and normality of residuals, revealed no indication of violation of assumptions.

We also analysed the association of isometric muscle strength with the odds of incident general overweight or obesity, abdominal obesity, raised BP, raised triglyceride and low HDL using multiple logistic regression adjusting for the same covariates as in the linear models. In these analyses we excluded prevalent cases of each respective risk factor at baseline. As the number of incident cases for some of the outcomes was low (eg, n=24 for raised BP) we performed a sensitivity analysis using propensity score matching[21] to comply with '≥10 outcome events per covariate' assumption including the same confounders as in the multivariable adjusted models. We did not proceed with analysing the risk of incident metabolic syndrome (according to AHA and NHLBI) and impaired fasting glucose in young adulthood, as the numbers of cases for these outcomes were <20.

Finally, we examined the association of isometric muscle strength in adolescence with cardiovascular risk in young

Table 1 Sex-adjusted baseline characteristics by tertiles of maximal voluntary isometric muscle strength in adolescence

	Isometric muscle strength in adolescence (tertiles)			
	0.71 (0.08) N/kg (n=110)	0.86 (0.08) N/kg (n=111)	1.04 (0.08) N/kg (n=111)	p Value
Age (years)	15.6 (0.4)	15.6 (0.4)	15.6 (0.4)	0.43
BMI (kg/m^2)	21.8 (2.6)	20.7 (2.5)	20.4 (2.6)	<0.001
Waist circumference (cm)	75.0 (6.4)	72.2 (6.2)	70.4 (6.6)	<0.001
Systolic BP (mm Hg)	109.7 (9.7)	110.0 (9.5)	108.4 (9.9)	0.44
Diastolic BP (mm Hg)	61.0 (6.6)	61.5 (6.4)	60.6 (6.7)	0.34
Triglyceride (mmol/l)	0.97 (0.47)	0.88 (0.46)	0.78 (0.48)	0.01
HDL-C (mmol/l)	1.40 (0.31)	1.42 (0.30)	1.41 (0.32)	0.86
Glucose (mmol/l)	5.16 (0.39)	5.10 (0.38)	4.97 (0.39)	0.002
Composite CVD risk z-score (SD)	0.89 (2.48)	0.01 (2.41)	−0.90 (2.53)	<0.001
Cardiorespiratory fitness (ml O_2/min/kg)	43.6 (5.5)	46.9 (5.4)	48.7 (5.6)	<0.001
Television watching (hours/day)	1.8 (1.1)	1.5 (1.1)	1.3 (1.1)	0.02
Soft drinks (servings/month)	7.9 (8.6)	9.2 (8.6)	10.4 (8.6)	0.10
Fruits and vegetables (servings/month)	34.1 (17.3)	37.7 (16.9)	43.9 (17.7)	<0.001
Parental education level (% 1/2/3)*	9.6/36.2/54.2	10.1/22.0/67.8	7.5/21.7/70.8	0.10
Family history of CVD (%)	34.1	35.3	24.7	0.22
Smoking (%)	13.1	14.8	16.7	0.79

Data are means (SD) or numbers (%) and are standardised according to the sex distribution of the study population.
*Based on educational level (International Standard Classification of Education (ISCED) (UNESCO 1997). The ISCED levels 1 and 2 were grouped, 3 and 4 were grouped and 5, 6 and 7 were grouped.
BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; N, Newton.

adulthood stratified by sex, follow-up time (6 or 12 years) and cardiorespiratory fitness level (sex-specific below or above the median of cardiorespiratory fitness).

We also performed additional sensitivity analyses to assess the robustness of our results. First, we repeated the analyses with the ratio of WC to height as outcome as an alternative to WC. Second, we repeated analyses using the absolute levels of isometric muscle strength and adjusted for body weight and in addition by scaling isometric muscle strength to body weight using the power of 2/3. Finally, because of the high attrition rate due to missing data and loss to follow-up we performed analyses comparing estimates of associations in the sample with complete data on covariates and outcomes (n=332) with the full sample (n=873) with missing values being imputed. We imputed missing values using a multivariate-chained equation imputation approach ('mi impute chained' in STATA) including all covariates and respective outomes. We obtained β coefficients and SE's based on 20 imputed datasets.[22]

All statistical analyses were performed in STATA V.12.1 with $\alpha=0.05$ (two-sided).

RESULTS

Individuals with missing data at baseline (including isometric muscle strength) or follow-up or that were lost to follow-up in 2009/2010 were not different according to age or sex distribution compared with participants in the present study with full data (see online supplementary table S1). However, differences were generally observed in baseline levels of CVD risk factors, lifestyle behaviours and a larger proportion was from parents with only a basic education among individuals lost to follow-up or with missing data. Table 1 shows the baseline characteristics of the study population by tertiles of isometric muscle strength in adolescence. Isometric muscle strength at baseline was negatively associated with BMI, WC, triglyceride, fasting glucose, composite CVD risk z-score and positively associated with intake of fruits and vegetables at baseline (all p<0.05). Isometric muscle strength and cardiorespiratory fitness in youth at baseline were modestly associated (figure 1). The sex-adjusted Pearson's correlation coefficient (r) between isometric muscle strength and cardiorespiratory fitness was 0.34 (95% CI 0.25 to 0.43), p<0.001.

Isometric muscle strength in youth was significantly associated with BMI, WC, triglyceride, HDL-C, diastolic BP and composite CVD risk factor score in young adulthood in age, sex and recruitment period-adjusted analyses and in multivariable-adjusted analyses except for WC (table 2). After additional adjustment for cardiorespiratory fitness, associations to BMI, triglyceride, DBP and CVD risk factor score persisted. Furthermore, associations also persisted with adjustment for WC, and using BMI instead of WC did not materially change these results (data not shown).

We also analysed the associations of youth abdominal or back strength relative to body weight separately with CVD risk factors in young adulthood. These analyses were very similar in

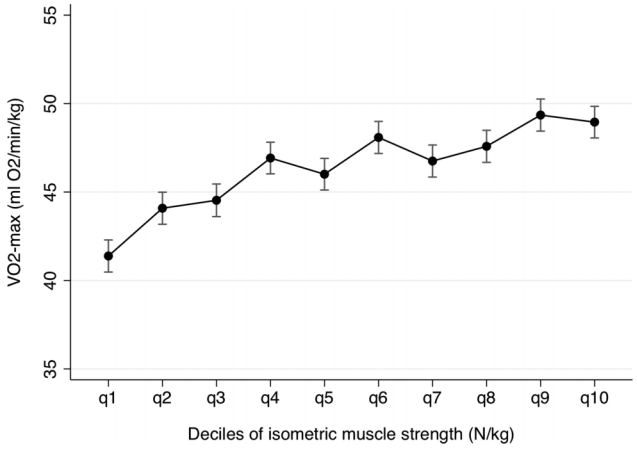

Figure 1 Association of isometric muscle strength and cardiorespiratory fitness in youth at baseline. Estimates are least SE from a sex-adjusted model. Deciles of isometric muscle strength are sex-specific.

Table 2 Isometric muscle strength in youth and cardiovascular risk factors in young adulthood

	Model 1 β (95% CI)	p Value	Model 2 β (95% CI)	p Value	Model 3 β (95% CI)	p Value	Model 4 β (95% CI)	p Value
Cardiovascular risk factor								
BMI (kg/m^2)	−0.50 (−0.86 to −0.14)	0.007	−0.45 (−0.81 to −0.08)	0.02	−0.60 (−0.97 to −0.22)	0.002	–	
Waist circumference (cm)	−1.09 (−2.10 to −0.08)	0.03	−0.97 (−2.00 to −0.06)	0.07	−0.93 (−2.00 to 0.13)	0.09	–	
Triglycerides (mmol/l)	−0.10 (−0.16 to −0.04)	0.002	−0.10 (−0.17 to −0.03)	0.004	−0.09 (−0.16 to −0.02)	0.01	−0.09 (−0.16 to −0.02)	0.01
HDL-C (mmol/l)	0.04 (0.01 to 0.07)	0.009	0.03 (0.0004 to 0.06)	0.04	0.02 (−0.01 to 0.05)	0.22	0.02 (−0.01 to 0.05)	0.27
Systolic BP (mm Hg)	−0.88 (−1.85 to 0.08)	0.07	−0.78 (−1.79 to 0.22)	0.13	−0.68 (−1.75 to 0.39)	0.21	−0.73 (−1.80 to 0.34)	0.18
Diastolic BP (mm Hg)	−1.34 (−2.17 to −0.50)	0.002	−1.24 (−2.11 to −0.37)	0.005	−1.22 (−2.15 to −0.29)	0.01	−1.25 (−2.18 to −0.32)	0.009
Glucose (mmol/l)	−0.05 (−0.10 to −0.002)	0.06	−0.05 (−0.10 to 0.003)	0.07	−0.04 (−0.09 to 0.01)	0.14	−0.04 (−0.09 to 0.01)	0.14
Composite CVD risk score (SD)	−0.75 (−1.14 to −0.36)	<0.001	−0.70 (−1.10 to −0.31)	0.001	−0.61 (−1.03 to −0.20)	0.004	−0.47 (−0.79 to −0.14)	0.005

β Coefficient (95% CI) represents change in risk factor in young adulthood per 1 SD (0.17 N/kg) change in isometric muscle strength in adolescence.
Model 1 was adjusted for baseline levels of risk factor, age at baseline, follow-up time, sex and recruitment period.
Model 2 was additionally adjusted for TV watching, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake and family history of CVD.
Model 3 was additionally adjusted for cardiorespiratory fitness.
Model 4 was additionally adjusted waist circumference. Waist circumference was not included in the composite CVD risk score in model 4.
BP, blood pressure; BMI, body mass index; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol.

magnitude to the mean of abdominal and back isometric strength (normalised to body weight). Furthermore, repeating analyses using the ratio of WC to height, using the absolute levels of isometric muscle strength and adjusting for body weight or by scaling isometric muscle strength to body weight using the power of 2/3 (N/kg$^{2/3}$) all gave fairly similar results (data not shown).

The analysis of isometric muscle strength and incident CVD risk factors is shown in figure 2. During an average of 8 years of follow-up from adolescence, 82, 32, 24, 36 and 55 number of incident cases of general overweight or obesity, abdominal obesity, raised BP, raised triglyceride levels, low HDL-C, respectively, occurred in young adulthood. In multivariable-adjusted analyses including cardiorespiratory fitness, each 1 SD of isometric muscle strength (0.17 N/kg) in youth was significantly associated with 0.59 (95% CI 0.40 to 0.87) lower odds of general overweight or obesity in young adulthood (p=0.007). Furthermore, isometric muscle strength in youth was marginally associated with incident raised BP, raised triglyceride and low HDL-C in young adulthood. Using propensity score matching to adjust for confounding did not materially change these results.

Multivariable-adjusted stratified analyses by sex, follow-up time (6 or 12 years) and cardiorespiratory fitness level are shown in figure 3. We did not see statistical evidence that the association of isometric muscle strength with composite CVD risk factor score were modified by these factors (p>0.1 for all interactions); however, stratified analyses indicated that associations were attenuated among individuals with low cardiorespiratory fitness (p=0.15 for interaction). Combined association of cardiorespiratory fitness and isometric muscle strength using sex-specific tertiles of fitness and strength, respectively, also

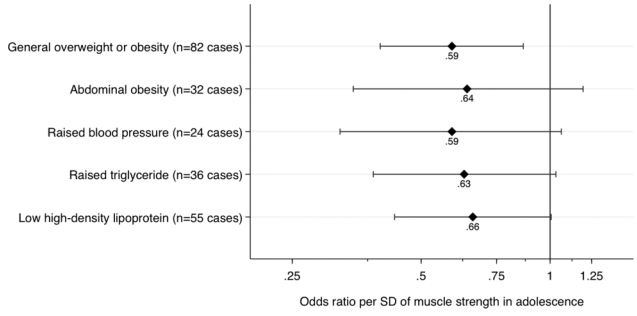

Figure 2 Isometric muscle strength in adolescence and risk of incident general overweight/obesity, abdominal obesity, raised blood pressure, raised triglyceride and low high-density lipoprotein in young adulthood. Estimates are ORs with 95% CI from logistic regression models adjusted for baseline levels of respective risk parameter (eg, body mass index for general overweight), age at baseline, follow-up time, sex, recruitment period, cardiorespiratory fitness, TV watching, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake and family history of cardiovascular disease. Numbers in brackets are incident cases of respective outcomes.

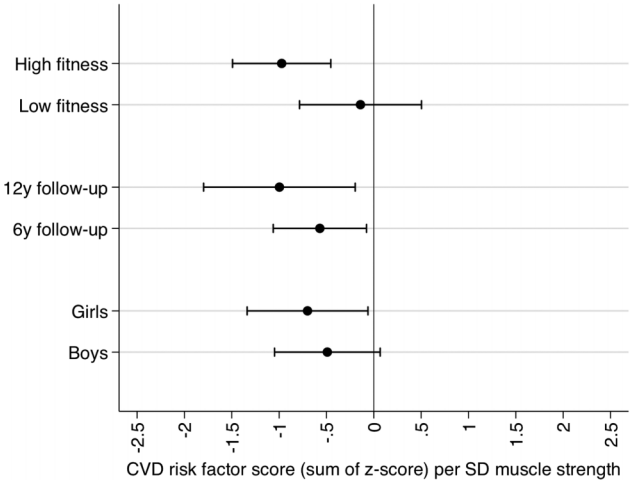

Figure 3 Isometric muscle strength in youth and composite cardiovascular risk factor score in young adulthood stratified by cardiorespiratory fitness (below and above the median, sex-specific), follow-up time (6 or 12 years) and sex. Estimates are β coefficients (composite cardiovascular disease (CVD) risk factor score in young adulthood per SD of isometric muscle strength in youth) from multivariable model adjusted for baseline levels of CVD risk score, age at baseline, follow-up time, sex, recruitment period, cardiorespiratory fitness, TV watching, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake and family history of CVD. Median of low fitness boys=46.5, girls=39.2; high fitness boys=54.7, girls=45.6.

indicated no interaction between strength and fitness on composite CVD score (p=0.22 for interaction) and suggested an additive effect of isometric muscle strength and fitness in youth on CVD risk in young adulthood. Participants being in the third sex-specific tertile of both fitness and strength had lowest composite CVD risk score in young adulthood (−1.42 SD (95% CI −2.67 to −0.17) compared with participants being in the first tertile of both fitness and strength).

Results from associations based on non-imputed samples (n=332) were fairly similar to imputed samples (see online supplementary table S2).

DISCUSSION

Results from this prospective population-based study suggest that greater isometric muscle strength of the abdomen and back in youth is associated with lower levels of CVD risk factors in young adulthood. These inverse associations were independent of cardiorespiratory fitness, adiposity and other sociodemographic and lifestyle factors. Our study supports including a specific recommendation for activities that increase muscle strength as part of the guidelines for PA in youth for primordial prevention of CVD risk later in life.

To the best of our knowledge this is the first study reporting independent associations of muscle strength with CVD risk factors among adolescents followed into adulthood. A previous study among children followed into adolescence has shown that improvement in handgrip strength during follow-up was associated with favourable changes in BP, lipid levels and adiposity independent of cardiorespiratory fitness.[23] A few prior cross-sectional studies among children or adolescents have reported similar findings. Two population-based studied among European children and adolescents have reported that muscle strength were associated with clustered metabolic risk independent of cardiorespiratory fitness.[24 25] Our results are also generally in line with findings from observational studies among adults. A report from the Aerobics Centre Longitudinal Study found that high dynamic muscle strength of the lower and upper body was associated with a decreased risk of premature mortality independent of cardiorespiratory fitness in men.[4] Furthermore, in the Health Professionals Follow-up Study men participating in weight training had a lower risk of CHD independent of other PA.[5] Other studies among adults have also reported inverse associations of muscle strength with premature mortality, but many have not adjusted for cardiorespiratory fitness.[26–29] Because we, and others, have reported that isometric muscle strength and cardiorespiratory fitness are modestly related, confounding by fitness is likely not trivial.

Numerous experimental studies support the biological plausibility of our findings. A number of small-scale randomised studies in overweight youth have provided evidence that muscle-strengthening exercise alone is beneficial for improving CVD risk factor levels.[30–33] Similarly, randomised trials among adults have shown beneficial effects of resistance training on BP, adiposity, glycemic control and triglyceride levels.[34–36] Because initiation in muscle-strengthening activities is strongly related to gains in muscle strength in youth,[9] these observations support our study and suggests that low muscle strength is causally related to development of unfavourable levels of CVD risk factors.

Our assessments of maximal isometric muscle strength of the abdomen and back were based on an easy, simple and fast testing procedure. Although previous studies have reported moderate-to-strong correlation between isometric and dynamic muscle strength,[37] further studies are warranted to confirm that assessment of muscle strength, using similar or alternative methods including different muscle groups and types of strength measures in predicting future CVD health outcomes independent of cardiorespiratory fitness. In addition, while the isometric muscle strength assessment procedures are very reliable in adults, we did not evaluate reliability of the tests in youth, which remains to be determined.

Strengths of this study include the prospective design, the standardised test for cardiorespiratory fitness and isometric muscle strength. Furthermore, the detailed collection of lifestyle factors, sociodemographic factors and other covariates allowed adjustment for several potential confounders. A number of possible limitations should also be considered. Although we observed substantial magnitudes of associations for isometric muscle strength, the sample size for the study was modest and the number of incident cases of CVD risk factor in young adulthood was not large in the logistic regression models. As a consequence the CIs for these analyses were wide, however, these analyses were supported by similar patterns in linear models. Although the composite CVD risk factor score has been widely used there are limitations to its use. Individual CVD risk factors are weighted equally in the composite score, is population-specific, and the predicate validity in youth for clinical health outcomes in adulthood remains unknown. Furthermore, as our study was observational, there will always be a possibility of unknown and residual confounding. Finally, the high attrition rate may have affected the generalisability of our findings and precluded us from adequately powered subgroup analysis. Since associations were fairly similar in imputed and non-imputed samples, this provides us some confidence that the results are not explained by selection bias.

In conclusion, greater isometric muscle strength of the abdomen and back in youth was associated with lower levels of CVD risk factors in young adulthood independent of cardiorespiratory fitness and other potential confounding factors. These results support a specific emphasis on participation in muscle-strengthening activities for primordial prevention of CVD risk in accordance to the current guidelines for PA in youth. Given the major global public health burden of CVD our results highlight the need to further investigate the role of participation in resistance training activities in other populations and in randomised trails in children and youth.

What this study adds

- This study suggests that greater isometric muscle strength of the abdomen and back in youth is associated with lower levels of cardiovascular risk factors in young adulthood independent of cardiorespiratory fitness, sociodemographic and lifestyle factors.

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Contributors AG collected the data, carried out the initial analyses, drafted the initial manuscript and approved the final manuscript as submitted. MR-L, NCM and PLK collected the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. KF conceptualised and designed the study, collected the data, reviewed and revised the manuscript, and approved the final manuscript as submitted. SB and LBA conceptualised and designed the study, reviewed and revised the manuscript and approved the final manuscript as submitted.

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REFERENCES

1 Ferreira I, Twisk JWR, van Mechelen W, *et al*. Development of fatness, fitness, and lifestyle from adolescence to the age of 36 years: determinants of the metabolic syndrome in young adults: the Amsterdam growth and health longitudinal study. *Arch Intern Med* 2005;165:42–8.
2 Kvaavik E, Klepp K-I, Tell GS, *et al*. Physical fitness and physical activity at age 13 years as predictors of cardiovascular disease risk factors at ages 15, 25, 33, and 40 years: extended follow-up of the Oslo youth study. *Pediatrics* 2009;123:e80–6.
3 Ruiz JR, Castro-Piñero J, Artero EG, *et al*. Predictive validity of health-related fitness in youth: a systematic review. *Br J Sports Med* 2009;43:909–23.
4 Ruiz JR, Sui X, Lobelo F, *et al*. Association between muscular strength and mortality in men: prospective cohort study. *BMJ* 2008;337:92–5.
5 Tanasescu M, Leitzmann MF, Rimm EB, *et al*. Exercise type and intensity in relation to coronary heart disease in men. *JAMA* 2002;288:1994–2000.
6 Grøntved A, Rimm EB, Willett WC, *et al*. A prospective study of weight training and risk of type 2 diabetes mellitus in men. *Arch Intern Med* 2012;172:1306–12.
7 World Health Organization. *Global recommendations on physical activity for health*. Geneva, Switzerland: WHO Press, 2010.
8 Physical activity guidelines advisory committee report. Washington, DC: U.S. Department of Health and Human Services, 2008. http://www.health.gov/paguidelines/guidelines/default.aspx
9 Behm DG, Faigenbaum AD, Falk B, *et al*. Canadian society for exercise physiology position paper: resistance training in children and adolescents. *Appl Physiol Nutr Metab* 2008;33:547–61.
10 Ortega FB, Silventoinen K, Tynelius P, *et al*. Muscular strength in male adolescents and premature death: cohort study of one million participants. *BMJ* 2012;345:e7279.
11 Riddoch C, Edwards D, Page A, *et al*. The European youth heart study—cardiovascular disease risk factors in children: rationale, aims, design and validation of methods. *J Phys Act Health* 2005;2:115–29.
12 Andersen LB, Henckel P. Maximal voluntary isometric strength in Danish adolescents 16–19 years of age. *Eur J Appl Physiol Occup Physiol* 1987;56:83–9.
13 Essendrop M, Schibye B, Hansen K. Reliability of isometric muscle strength tests for the trunk, hands and shoulders. *Int J Ind Ergon* 2001;28:379–87.
14 Kolle E, Steene-Johannessen J, Andersen LB, *et al*. Objectively assessed physical activity and aerobic fitness in a population-based sample of Norwegian 9- and 15-year-olds. *Scand J Med Sci Sports* 2010;20:e41–7.
15 Anderssen SA, Cooper AR, Riddoch C, *et al*. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. *Eur J Cardiovas Prev Rehabil* 2007;14:526–31.
16 Grøntved A, Ried-Larsen M, Møller NC, *et al*. Youth screen-time behaviour is associated with cardiovascular risk in young adulthood: the European youth heart study. *Eur J Prev Cardiol* 2012;(in press).
17 Ekelund U, Brage S, Froberg K, *et al*. TV viewing and physical activity are independently associated with metabolic risk in children: the European youth heart study. *PLoS Med* 2006;3:e488.
18 Grundy SM, Cleeman JI, Daniels SR, *et al*. Diagnosis and management of the metabolic syndrome. *Circulation* 2005;112:2735–52.
19 Brage S, Wedderkopp N, Ekelund U, *et al*. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). *Diabetes Care* 2004;27:2141–8.
20 Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel iii) final report. *Circulation* 2002;106:3143.
21 Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J* 2011;32:1704–8.
22 Royston P. Multiple imputation of missing values. *Stata J* 2004;4:227–41.
23 Janz KF, Dawson JD, Mahoney LT. Increases in physical fitness during childhood improve cardiovascular health during adolescence: the Muscatine study. *Int J Sports Med* 2002;23:15–21.
24 Steene-Johannessen J, Anderssen SA, Kolle E, *et al*. Low muscle fitness is associated with metabolic risk in youth. *Med Sci Sports Exerc* 2009;41:1361–7.
25 Artero EG, Ruiz JR, Ortega FB, *et al*. Muscular and cardiorespiratory fitness are independently associated with metabolic risk in adolescents: the Helena study. *Pediatr Diabetes* 2011;12:704–12.
26 Rantanen T, Harris T, Leveille SG, *et al*. Muscle strength and body mass index as long-term predictors of mortality in initially healthy men. *J Gerontol Series A* 2000;55:M168–73.
27 Metter EJ, Talbot LA, Schrager M, *et al*. Skeletal muscle strength as a predictor of all-cause mortality in healthy men. *J Gerontol Series A* 2002;57:B359–65.
28 Katzmarzyk PT, Craig CL. Musculoskeletal fitness and risk of mortality. *Med Sci Sports Exerc* 2002;34:740–4.
29 Newman AB, Kupelian V, Visser M, *et al*. Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. *J Gerontol Series A* 2006;61:72–7.
30 Van Der Heijden GJ, Wang ZJ, Chu Z, *et al*. Strength exercise improves muscle mass and hepatic insulin sensitivity in obese youth. *Med Sci Sports Exerc* 2010;42:1973–80.
31 Suh S, Jeong IK, Kim MY, *et al*. Effects of resistance training and aerobic exercise on insulin sensitivity in overweight Korean adolescents: a controlled randomized trial. *Diabetes Metab J* 2011;35:418–26.
32 Benson AC, Torode ME, Singh MA Fiatarone. The effect of high-intensity progressive resistance training on adiposity in children: a randomized controlled trial. *Int J Obes (Lond)* 2008;32:1016–27.
33 Benson AC, Torode ME, Singh MA Fiatarone. Effects of resistance training on metabolic fitness in children and adolescents: a systematic review. *Obes Rev* 2008;9:43–66.
34 Cornelissen VA, Fagard RH, Coeckelberghs E, *et al*. Impact of resistance training on blood pressure and other cardiovascular risk factors. *Hypertension* 2011;58:950–8.
35 Umpierre D, Ribeiro PAB, Kramer CK, *et al*. Physical activity advice only or structured exercise training and association with hba1c levels in type 2 diabetes. *JAMA* 2011;305:1790–9.
36 Williams MA, Haskell WL, Ades PA, *et al*. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American heart association council on clinical cardiology and council on nutrition, physical activity, and metabolism. *Circulation* 2007;116:572–84.
37 Juneja H, Verma SK, Khanna GL. Isometric strength and its relationship to dynamic performance: a systematic review. *J Exerc Sci Physiother* 2010;6:60–9.

Table 1. Attrition analysis by baseline characteristics.

	Participants (n=332)	Individuals with missing data or lost to follow-up (n=541 or lower)	p
Age (years)	15.6 (0.4)	15.6 (0.4) (n=541)	0.17
Gender (% boys)	48.2	44.2 (n=541)	0.25
BMI (kg/m^2)	21.0 (2.6)	21.1 (3.0) (n=541)	0.62
Waist circumference (cm)	72.5 (6.7)	71.5 (7.7) (n=540)	0.05
Systolic BP (mmHg)	109.4 (10.1)	111.4 (10.5) (n=541)	0.005
Diastolic BP (mmHg)	61.4 (6.4)	62.7 (6.2) (n=541)	0.003
Triglyceride (mmol/l)	0.88 (0.46)	0.94 (0.42) (n=500)	0.03
HDL-C (mmol/l)	1.41 (0.31)	1.37 (0.31) (n=500)	0.11
Glucose (mmol/l)	5.08 (0.40)	5.14 (0.48) (n=500)	0.06
Cardiorespiratory fitness (ml O_2/min/kg)	46.4 (7.0)	45.6 (8.2) (n=474)	0.18
Isometric muscle strength (N/kg)	0.87 (0.16)	0.85 (0.18) (352)	0.15
Television viewing (hours/day)	1.5 (1.1)	1.8 (1.2) (n=529)	0.002
Soft drinks (servings/month)	9.2 (8.7)	11.1 (9.4) (n=529)	0.002
Fruits and vegetables (servings/month)	38.6 (17.5)	37.2 (17.2) (n=529)	0.24
Parental education level (% 1 / 2 / 3)*	9.0 / 26.5 / 64.5	14.9 / 32.9 / 52.3 (n=505)	0.001
Family history of CVD (%)	31.3	27.2 (n=515)	0.19
Smoking (%)	14.8	27.0 (n=529)	<0.001

Data are means (SD) or numbers (%).

*Based on educational level (International Standard Classification of Education (ISCED) (UNESCO 1997). The ISCED level 1 and 2 were grouped, 3 and 4 were grouped, and 5, 6 and 7 were grouped.

Table 2. Association of isometric muscle strength in youth with cardiovascular risk factors in young adulthood from the imputed analyses of the total sampled population at baseline (n=873). Imputations were performed using chained equations ("mi impute chained" in STATA). All covariates and respective outomes were included in the imputation approach. Beta coefficients and SE's were based on 20 imputed datasets.

	Beta (95% CI)	P
Cardiovascular risk factor		
BMI (kg/m^2)	-0.51 (-0.92;-0.10)	0.02
Waist circumference (cm)	-1.03 (-2.16;-0.11)	0.08
Triglycerides (mmol/l)	-0.09 (-0.16;-0.02)	0.01
HDL-C (mmol/l)	0.02 (-0.01;0.06)	0.16
Systolic BP (mmHg)	-0.67 (-1.94;0.61)	0.29
Diastolic BP (mmHg)	-1.31 (-2.20;-0.42)	0.005
Glucose (mmol/l)	-0.05 (-0.11;-0.002)	0.06
Composite CVD risk score (SD)	-0.61 (-0.94;-0.28)	<0.001

Beta coefficient (95% CI) represents change in risk factor in young adulthood per 1 SD (0.17 N/kg) change in muscle strength in adolescence.

Models were adjusted for baseline levels of risk factor, age at baseline, age at follow-up, gender, cohort, TV-viewing, parental education level, smoking status, intake of soft drinks, fruit- and vegetable intake, family history of CVD, and cardiorespiratory fitness.

Paper V

Grøntved A, Ried-Larsen M, Ekelund U, Froberg K, Brage S, Andersen LB. Independent and combined association of muscle strength and cardiorespiratory fitness in youth with insulin resistance and beta-cell function in young adulthood (The European Youth Heart Study). *Diabetes Care.* 2013. (Epub ahead of print).

Independent and Combined Association of Muscle Strength and Cardiorespiratory Fitness in Youth With Insulin Resistance and β-Cell Function in Young Adulthood

The European Youth Heart Study

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OBJECTIVE—To examine the independent and combined association of isometric muscle strength of the abdomen and back and cardiorespiratory fitness (CRF) in youth with indices of glucose metabolism in young adulthood among boys and girls from the European Youth Heart Study.

RESEARCH DESIGN AND METHODS—We used data from a population-based prospective cohort study among youth followed-up for up to 12 years (n = 317). In youth, maximal voluntary contractions during isometric back extension and abdominal flexion were determined using a strain-gauge dynamometer and CRF was obtained from a maximal cycle ergometer test. Insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) and β-cell function (homeostasis model assessment of β-cell function [HOMA-B]) were estimated from fasting serum insulin and glucose that were obtained in youth and at follow-up in young adulthood.

RESULTS—For each 1-SD difference in isometric muscle strength (0.16 N/kg) in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed with −11.3% (95% CI, −17.0 to −5.2), −12.2% (−18.2 to −5.7), and −8.9% (−14.4 to −3.0), respectively, in young adulthood after adjustment for CRF and personal lifestyle and demographic factors. Results for CRF were very similar in magnitude, and the magnitude of associations for both exposures was unchanged with additional adjustment for general or abdominal adiposity in youth. Combined associations of muscle strength and CRF with fasting insulin, HOMA-IR, and HOMA-B were additive, and adolescents in the highest sex-specific tertile for both isometric muscle strength and CRF had the lowest levels of these glucose metabolism outcomes.

CONCLUSIONS—Increasing muscle strength and CRF should be targets in youth primordial prevention strategies of insulin resistance and β-cell dysfunction.

Previously, type 2 diabetes was very rare in young people. Today, it is more common not only in young adults but also in youth, and a similar trend has been observed for impaired fasting glucose and impaired glucose tolerance (1–3), which are considered precursors of type 2 diabetes. Youth and young adults with type 2 diabetes or prediabetes are at risk for premature mortality and early complications (4,5), making prevention critical. Numerous prospective epidemiological studies among adults suggest that regular participation in aerobic moderate-to-vigorous physical activity (MVPA) and high cardiorespiratory fitness (CRF) reduce the risk of type 2 diabetes and are associated with healthier glucose metabolism (6,7). However, less is known from prospective studies about the importance of fitness in childhood and adolescence (8). In addition, it is unknown whether muscle strength in youth is associated with impaired glucose metabolism in adulthood independent of CRF. In this study, we aimed to examine the independent and combined association of isometric muscle strength of the abdomen and back and CRF in youth with fasting glucose, insulin, insulin resistance, and β-cell function in young adulthood among men and women from the European Youth Heart Study (EYHS) followed-up for a period of up to 12 years. We also assessed the extent to which these associations were mediated or confounded by general and abdominal adiposity.

RESEARCH DESIGN AND METHODS

Design

We used data from the Danish cohort of the EYHS, an international, population-based, multicenter study that addresses cardiovascular disease risk factors in children and adolescents. A detailed description of the EYHS has been published elsewhere (9). In this study a random sample of 658 15-year-olds were invited to participate in 1997–1998, of whom 429 (65%) agreed to take part in the study. Isometric muscle strength was assessed in a subgroup of 243 participants in 1997–1998. In 2003–2004, another random sample of 771 15-year-olds was invited, of whom 444 (58%) agreed to take part, and 441 of these participants had isometric muscle strength evaluated. In 2009–2010, a 6- or 12-year follow-up was conducted in which all originally

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invited participants from the 1997–1998 and 2003–2004 studies were reinvited. In this study, 317 participants had complete data for all outcomes, exposures, and covariates. Ninety-four percent of the participants were postpubertal based on Tanner stage evaluation. The local scientific Ethics Committee approved the study and all participants gave informed consent to participate.

Muscle strength

We obtained isometric muscle strength during maximal voluntary contraction of abdominal and back muscles using a strain-gauge dynamometer (10). The participants were standing upright and positioned with a strap around the shoulders connected to the dynamometer. Abdominal maximal voluntary contraction was performed with the back against the dynamometer performing maximal forward flexion. For maximal voluntary contraction of the low back muscles, the participants were positioned with the front against the dynamometer, performing maximal backward extension. Isometric muscle strength was expressed as the mean of abdominal and back strength relative to body weight. High reliability of these particular isometric strength measures (intraclass correlation coefficient >0.9) has been reported in a previous study among Danish adults (11).

Cardiorespiratory fitness

CRF was assessed during a progressive maximal ergometer bicycle test (Ergomedic 839; Monark, Varberg, Sweden) as previously described (9). During the test, heart rate was recorded every 5 s using a heart rate monitor (Polar Vantage). Criteria for maximal effort were heart rate of ≥185 bpm and a subjective judgment by the observer that the participant could no longer continue, even after encouragement. Maximal power output ($watt_{max}$) was used to estimate maximal oxygen uptake using the following equation: VO_{2max} (mL) = 0.465 + (0.0112*$watt_{max}$) + (0.172*sex), where sex represents boys = 1 and girls = 0 (12). This particular fitness test is highly reproducible (coefficient of variation 2.5–4.8%). Furthermore, a validation study among 15-year-olds has shown that this measure is highly correlated with VO_{2max} assessed directly ($r > 0.90$; $P < 0.001$) (13).

Other covariates

Height and weight were measured while the participants were wearing light clothing, without shoes, using standard anthropometric procedures. Waist circumference was measured to the nearest 1 mm at the midpoint between the lower ribs and the iliac crest with a flexible tape. Smoking status (yes or no), television viewing (hours per day), monthly frequency of soft drink consumption, and monthly fruit and vegetable intake were obtained by self-report of adolescence using a computer-based questionnaire as described previously (9,14). Family history of diabetes (paternal or maternal, yes or no) and parental educational level were obtained by parental self-report. Parental educational status was defined according to the International Standard Classification of Education (United Nations Educational, Scientific, and Cultural Organization 1997). However, because the details obtained regarding the description of education were insufficient, the International Standard Classification of Education seven-point scale was combined into three new groups (I = level 1–2; II = level 3–4; and III = level 5–7). MVPA was assessed using accelerometry with data reduction as described previously (15). Specifically, an accelerometer output >2,000 counts/min (equivalent to walking ~4 km/h) was defined as MVPA and expressed as percentage of total registered time. Weight-bearing activity such as resistance exercise is grossly underestimated when using accelerometry-measured activity.

Fasting insulin and glucose

A fasting blood sample (overnight) was taken in the morning from the antecubital vein. Samples were aliquoted and separated within 30 min, and then stored at −80°C until they were transported to World Health Organization–certified laboratories in Bristol (United Kingdom) for analysis of baseline samples and Cambridge (United Kingdom) for analysis of follow-up samples. Samples were analyzed for serum glucose and insulin. Glucose was analyzed using the hexokinase method (Olympus AU600 autoanalyzer; Olympus Diagnostica, Hamburg, Germany) at baseline and on a Dade Behring Dimension RxL autonalyzer (Siemens Healthcare, Camberley, UK) at follow-up. Insulin was analyzed using enzyme immunoassay (microtiter plate format, Dako Diagnostics [at baseline]; 1235 AutoDELFIA automatic immunoassay [at follow-up]). Between-laboratory correlations for glucose and insulin for 30 randomly selected samples analyzed at both laboratories were 0.94–0.98 at baseline (16).

The homeostasis model assessment of insulin resistance (HOMA-IR; fasting glucose [mmol/L] × insulin [μU/mL] / 22.5) and homeostasis model assessment of β-cell function (HOMA-B; insulin [μU/mL] × 20 / glucose [mmol/L] − 3.5) were used to quantify the level of insulin resistance and secretion (17). Both these measures have been validated as indices of insulin resistance and pancreatic β-cell function in healthy adolescents (18).

Statistics

We analyzed the associations of isometric muscle strength and CRF in adolescence with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood using multiple linear regression analyses with baseline levels of respective variables included as a covariate. In basic models, age in adolescence, age in young adulthood, sex, and recruitment period were adjusted for. Values of insulin, HOMA-IR, and HOMA-B were natural log–transformed. Thus, regression coefficients from these models were exponentiated to give ratios of geometric means (expressed in percent) per SD difference in isometric muscle strength and CRF. In multivariable analyses, we additionally adjusted for parental educational level, current smoking, family history of diabetes, frequency of intake of soft drinks, and intake of fruit and vegetables. Muscle strength and CRF in youth also were included in the same model to examine their independent influence on glucose, insulin, HOMA-IR, and HOMA-B in young adulthood. We then analyzed the association of muscle strength with the odds of insulin resistance, defined as HOMA-IR value >75th percentile in young adulthood (19), using multiple logistic regression adjusting for the same covariates as in the linear models including HOMA-IR at baseline. Finally, we assessed the joint association of muscle strength and CRF by constructing a joint variable of tertiles of muscle strength and CRF, respectively, and associated that with the outcomes in multivariable models. Because no sex-dependent or recruitment period–dependent associations for any outcomes were observed, we present all analyses for men, women, and recruitment period (follow-up time) combined, but with appropriate statistical adjustment. Standard linear regression diagnostics were performed, including examining linearity and normality of residuals.

In sensitivity analyses, we compared associations of the nonimputed sample

with a sample with imputed data. We imputed missing information for covariates and outcomes (n = 12 to n = 556, depending on variable) among the total sampled population at baseline (n = 873) using chained equations ("mi impute chained" in STATA) (20). All covariates and respective outcomes were included in the imputation approach. We obtained β coefficients and SEs based on 20 imputed datasets. We also performed an analysis additionally adjusting for accelerometry-measured MVPA to examine if any residual confounding by MVPA remained that CRF may not have captured. Because 35% of the participants with otherwise full data had missing information regarding accelerometer-measured MVPA, we imputed missing values for MVPA using a multiple linear regression imputation approach including all covariates and the outcome. All statistical analyses were performed in STATA 12.1 with α=0.05 (two-sided).

RESULTS—Baseline characteristics adjusted for sex by tertiles of isometric muscle strength in adolescence are shown in Table 1. Isometric muscle strength in adolescence was inversely associated with adolescence BMI, waist circumference, fasting glucose, fasting insulin, HOMA-IR, and television viewing, and was positively associated with cardiovascular fitness and intake of fruits and vegetables at baseline.

Isometric muscle strength and CRF in youth were both significantly inversely associated with fasting insulin, HOMA-IR, and HOMA-B in young adulthood in multivariable-adjusted analyses (Table 2). Although associations of adolescent muscle strength and CRF with fasting glucose in young adulthood were in the expected inverse direction, these did not reach statistical significance. When muscle strength and CRF were included in the same multivariable models, associations with insulin, HOMA-IR, and HOMA-B were only marginally attenuated for both variables. For each 1-SD difference in muscle strength (0.16 N/kg) in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed −11.3, −12.2, and −8.9%, respectively. The magnitudes of associations for CRF were fairly similar; for each SD difference in CRF in youth, fasting insulin, HOMA-IR, and HOMA-B in young adulthood changed −12.8, −13.3, and −10.0%, respectively. When we additionally adjusted our analyses for waist circumference measured at baseline, estimates of associations were only slightly attenuated for both exposures (Table 2, model 4). Using BMI instead of waist circumference as a confounder or mediator gave the same results (data not shown). Furthermore, additional adjustment for accelerometer-measured MVPA did not materially change the associations (data not shown). When we repeated the analyses based on imputed samples (n = 873), associations were essentially similar to the nonimputed analyses (Supplementary Table 1). Analyzing isometric abdominal and back strength separately also yielded fairly similar associations compared with using the mean of abdominal and back isometric strength (Supplementary Table 2).

For the association of muscle strength and CRF in youth (in the same multivariable-adjusted model) with the odds of insulin resistance in young adulthood, each 1-SD difference in muscle strength (0.16 N/kg) and CRF (6.8 mL O_2/min/kg) in youth was significantly associated with 0.56 (95% CI, 0.39–0.81) and 0.63 (0.43–0.94) lower odds of adverse levels of HOMA-IR in young adulthood, respectively. Participants in the third sex-specific tertile of isometric muscle strength had 0.31 (0.15–0.66) lower odds of insulin resistance in young adulthood. Furthermore, participants in the third sex-specific tertile of CRF had 0.48 (0.23–1.01) lower odds of insulin resistance in young adulthood. There were no indications of the associations of muscle strength or CRF with HOMA-IR being nonlinear in these models.

Finally, Table 3 shows the joint associations of isometric muscle strength and CRF in adolescence with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood. The inverse associations of isometric muscle strength with insulin, HOMA-IR, and HOMA-B in young adulthood were generally observed in each tertile of CRF. There was no statistical evidence of multiplicative interactions between muscle strength and CRF on these outcomes, and results suggested an additive effect of muscle strength and CRF on glucose metabolism outcomes.

CONCLUSIONS—In this prospective study of a population sample of Danish men and women, isometric muscle strength and CRF in youth were inversely associated with fasting insulin, and inversely associated with markers of insulin

Table 1—*Baseline characteristics adjusted for sex by tertiles of maximal voluntary isometric trunk muscle strength in adolescence*

	Muscle strength in adolescence (tertiles)			
	0.71 (0.08) N/kg (n = 105)	0.86 (0.08) N/kg (n = 106)	1.04 (0.09) N/kg (n = 106)	P
Age, years	15.6 (0.4)	15.6 (0.4)	15.6 (0.4)	0.57
BMI, kg/m^2	21.9 (2.6)	20.6 (2.5)	20.4 (2.6)	<0.001
Waist circumference, cm	75.3 (6.4)	72.0 (6.2)	70.5 (6.5)	<0.001
Glucose, mmol/L	5.17 (0.39)	5.11 (0.38)	4.98 (0.39)	0.002
Log insulin, pmol/L	2.29 (0.46)	2.21 (0.45)	2.04 (0.47)	0.001
Log HOMA-IR	0.82 (0.49)	0.72 (0.48)	0.53 (0.50)	<0.001
Log HOMA-B	4.80 (0.46)	4.76 (0.45)	4.70 (0.47)	0.17
Cardiorespiratory fitness, mL O_2/min/kg	43.5 (5.5)	46.8 (5.4)	48.6 (5.6)	<0.001
Television viewing, h/day	1.8 (1.1)	1.6 (1.1)	1.3 (1.1)	0.01
Soft drinks, servings/month	8.7 (8.4)	9.4 (8.2)	9.4 (8.6)	0.79
Fruits and vegetables, servings/month	35.1 (17.2)	37.2 (16.8)	44.5 (17.6)	<0.001
Smoking status, %	12.0	13.7	14.3	0.88
Parental education level, % I/II/III*	6.8/36.1/57.0	9.5/22.1/68.4	7.2/20.9/71.9	0.13
Family history of diabetes, %	1.8	1.9	7.2	0.13

Data are means (SD) or numbers (%) adjusted for sex. *Based on educational level (International Standard Classification of Education (United Nations Educational, Scientific, and Cultural Organization 1997). I = basic education; II = secondary or postsecondary education; and III = tertiary education.

Table 2—*Isometric trunk muscle strength and cardiorespiratory fitness in youth and fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood*

	Model 1		Model 2		Model 3		Model 4	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Muscle strength								
Glucose*	−0.03 (−0.08 to 0.02)	0.21	−0.03 (−0.08 to 0.02)	0.27	−0.02 (−0.08 to 0.03)	0.41	−0.02 (−0.08 to 0.03)	0.40
Insulin†	−15.3 (−20.4 to −9.0)	<0.001	−14.6 (−20.0 to −9.0)	<0.001	−11.3 (−17.0 to −5.2)	<0.001	−11.2 (−16.9 to −5.0)	0.001
HOMA-IR†	−16.3 (−21.7 to −10.5)	<0.001	−15.6 (−21.2 to −9.5)	<0.001	−12.2 (−18.2 to −5.7)	<0.001	−12.1 (−18.2 to −5.6)	<0.001
HOMA-B†	−12.1 (−17.0 to −6.9)	<0.001	−11.8 (−16.8 to −6.4)	<0.001	−8.9 (−14.4 to −3.0)	0.004	−8.8 (−14.3 to −2.9)	0.004
Cardiorespiratory fitness								
Glucose*	−0.04 (−0.09 to 0.01)	0.16	−0.03 (−0.08 to 0.03)	0.30	−0.02 (−0.08 to 0.04)	0.48	−0.02 (−0.09 to 0.05)	0.49
Insulin†	−17.0 (−22.7 to −10.9)	<0.001	−16.6 (−22.5 to −10.2)	<0.001	−12.8 (−19.2 to −5.8)	0.001	−11.4 (−19.0 to −3.2)	0.008
HOMA-IR†	−17.8 (−23.9 to −11.3)	<0.001	−17.3 (−23.6 to −10.5)	<0.001	−13.3 (−20.1 to −5.9)	0.001	−12.1 (−20.1 to −3.2)	0.009
HOMA-B†	−13.2 (−18.7 to −7.4)	<0.001	−13.2 (−18.8 to −7.2)	<0.001	−10.0 (−16.1 to −3.4)	0.004	−9.2 (−16.5 to −1.4)	0.02

Model 1 was adjusted for baseline levels of risk factor, age, sex, and recruitment period. Model 2 was as model 1 but with additional adjustment for television viewing, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake, and family history of diabetes. Model 3 was as model 2 and included both muscle strength and CRF (mutually adjusted). Model 4 was as model 3 but with additional adjustment for waist circumference. *Beta coefficient (95% CI) represents mmol/L change in glucose in young adulthood per each 1-SD difference in muscle strength or CRF in adolescence. †Beta coefficient (95% CI) represents change in ratios of geometric means (expressed in percentage) in insulin, HOMA-IR, or HOMA-B in young adulthood per each 1-SD difference in muscle strength or CRF in adolescence.

resistance and β-cell function in young adulthood. These associations were independent of adiposity and demographic, personal, and lifestyle factors, and they suggest that muscle strength in youth is equally important as CRF for maintaining healthy insulin sensitivity and β-cell function later in life.

The current guidelines for physical activity among children and adults recommend participation in activities that maintain or increase muscular strength and endurance ≥2 days (adults) or ≥3 days (children and adolescents) each week in addition to participation in aerobic MVPA (≥30 min/day for adults and ≥60 min/day for youth) (21,22). Our results generally support these guidelines; however, they also suggest that an even greater emphasis could be placed on maintaining or increasing muscle strength among youth. Because associations between CRF and strength with insulin resistance and β-cell function were independent of each other, this supports the view that aerobic activities and muscle strengthening activities should be targeted separately. Furthermore, the analyses of continuous trait and binary outcomes suggested that muscle strength and CRF were linearly associated with fasting insulin, insulin resistance, and β-cell function, indicating that there is no clear threshold effect of an increase in insulin secretion or action at a particular low level of fitness or muscle strength. Efforts to shift the population distribution of muscle strength and CRF upwards are therefore likely to be valuable for primordial prevention of type 2 diabetes.

We are aware of three randomized controlled trials conducted among youth comparing the effect of resistance training on insulin resistance or glycemic control with a pure control group. A small-scale trial among 22 overweight Latino adolescent males found that 16 weeks of resistance training performed twice per week markedly increased insulin sensitivity (23). Another randomized trial among 78 overweight or obese children and adolescents from New Zealand reported that the effect of 8 weeks of resistance training performed twice per week had no significant effect on insulin resistance; however, results were in the expected direction and the training improved abdominal and general adiposity (24). A recent efficacy trial among 45 obese adolescent boys reported that both aerobic exercise and resistance training were effective for reducing adiposity, but only

Table 3—*Joint association of sex-specific tertiles of isometric trunk muscle strength and cardiorespiratory fitness in adolescence with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood*

	Cardiorespiratory fitness (mL O_2/min/kg)			
	Least square means or ratio of geometric means (95% CI)			
Isometric muscle strength, N/kg	1st tertile	2nd tertile	3rd tertile	*P*
Glucose				
1st tertile	5.05 (4.49–5.15)	5.17 (5.02–5.32)	5.01 (4.85–5.17)	0.26
2nd tertile	5.09 (4.94–5.23)	5.02 (4.90–5.14)	5.03 (4.91–5.16)	
3rd tertile	5.00 (4.83–5.17)	5.08 (4.96–5.20)	4.97 (4.85–5.08)	
Insulin				
1st tertile	0 (reference)	−2.7 (−23.2 to 23.2)	−22.3 (−39.9 to 0.43)	0.28
2nd tertile	6.0 (−15.9 to 33.6)	−18.1 (−33.7 to 1.2)	−29.0 (−42.7 to −11.8)	
3rd tertile	−31.4 (−47.0 to −11.1)	−30.9 (−44.2 to −14.5)	−32.1 (−44.8 to −16.5)	
HOMA-IR				
1st tertile	0 (reference)	−0.8 (−23.0 to 27.8)	−23.8 (−42.2 to 0.3)	0.30
2nd tertile	6.3 (−17.0 to 36.2)	−18.6 (−35.0 to 2.0)	−29.9 (−44.5 to −11.5)	
3rd tertile	−32.9 (−49.2 to −11.1)	−31.3 (−45.4 to −13.6)	−34.2 (−47.4 to −17.8)	
HOMA-B				
1st tertile	0 (reference)	−9.5 (−27.3 to 12.7)	−13.1 (−31.3 to 9.9)	0.62
2nd tertile	4.9 (−15.4 to 30.0)	−16.7 (−31.5 to 1.2)	−27.5 (−40.7 to −11.3)	
3rd tertile	−24.7 (−40.8 to −4.3)	−29.8 (−42.3 to −14.6)	−25.3 (−38.2 to −9.6)	

Estimates are least square means (fasting glucose) or ratios of geometric means expressed in percent (insulin, HOMA-IR, and HOMA-B) adjusted for baseline levels of the outcome, age at baseline, age at follow-up, sex, recruitment period, television viewing, parental education level, smoking status, intake of soft drinks, fruit and vegetable intake, and family history of diabetes.

the resistance exercise group improved insulin sensitivity (25). Although we have no data to support that participants with high isometric muscle strength of the abdomen and back engage more often in muscle-strengthening activities compared with participants with low muscle strength, findings from these and other exercise training studies clearly indicate that resistance training increases muscular strength (26). Our results are also largely in agreement with three previous cross-sectional studies among children and adolescents. A population-based study among Norwegian children and adolescents found that muscle fitness indicated by handgrip strength, standing broad jump, abdominal muscle endurance, and back muscle endurance were inversely associated with insulin resistance–independent of CRF (27). A study among European children and adolescents have reported inverse associations of handgrip strength and standing long jump with insulin resistance; however, it was not reported if these associations were independent of cardiovascular fitness (28). Finally, in a cross-sectional study among children and adolescents from New Zealand, maximal upper body muscle strength (bench press) was inversely associated with insulin resistance–independent of CRF (29). Our results extend these previous observations by the prospective nature of our study and the adjustments for putative lifestyle behaviors and sociodemographic confounders. The finding that CRF in childhood or youth is important for the prevention of insulin resistance in adulthood is supported by a previous study among Australian children and adolescents followed-up for a period of 20 years (8).

The similar magnitude of association of muscle strength and cardiovascular fitness with insulin resistance that we observed in the current study is in agreement with findings from experimental and observational studies among adults. The two largest trials among individuals with type 2 diabetes have not provided clear evidence that aerobic exercise is superior to resistance exercise for glycemic control (30,31). However, these studies indicated that the combination of aerobic and resistance exercise results in greatest improvement in glycemic control compared with either type of activity alone. The comparable effects of these two exercise regimes are also supported by a recent experimental study reporting that a single session of either aerobic or resistance exercise provided similar effects on 24-h postexercise glycemic control in insulin-resistant individuals with and without type 2 diabetes (32). Finally, in a prospective study of men from the Health Professionals Follow-up study, engagement in weight training and aerobic MVPA were both independently associated with reduced risk of incident type 2 diabetes with fairly comparable risk reduction sizes (33).

An important strength of the current study was that we were able to examine the independent associations for strength and CRF, and we were able to control for important confounding factors. Furthermore, all participants were young and healthy at baseline and, therefore, very likely to be free from subclinical conditions that may have affected muscle strength at baseline and progression of insulin resistance and β-cell dysfunction during follow-up. There are also a number of limitations to the study. First, the attrition analyses indicated a possibility of selective nonresponse; however, associations were very similar in imputed and nonimputed samples, which suggests that associations are unaffected by selection bias, and our results may have wider external validity. Second, the moderate study size precluded us from adequately powered subgroup analysis. Third, although we used a standardized test for the assessment of isometric muscle strength of the abdomen and back,

additional components of strength such as dynamic strength also may be important and their assessment would have provided more extensive information on overall muscle strength. Fourth, the observational nature of our study precludes us from excluding the possibility that unknown confounders or residual confounding explain our results. One such likely factor is diet, because the assessment of dietary intake was relatively crude in this study. Finally, a caveat of the study was that we assessed insulin resistance and β-cell function via HOMA-IR and HOMA-B, which mainly describe hepatic insulin resistance and steady-state insulin secretion, and generalizability to peripheral insulin resistance and insulin secretion in the stimulated state is uncertain (34).

In conclusion, our results show that lower isometric muscle strength and CRF in youth were independently associated with adverse levels of fasting insulin, insulin sensitivity, and β-cell function in young adulthood. The magnitude of associations for isometric muscle strength and for CRF were very similar, suggesting that participation in muscle-strengthening activities may be equally important as participating in aerobic activities in youth for maintaining healthy insulin sensitivity and β-cell function later in life. Furthermore, because associations for isometric muscle strength and CRF with these outcomes appeared additive, it may be beneficial to increase muscle strength at any level of CRF. Further studies are warranted to examine which specific physical activities explain the associations of isometric muscle strength with insulin sensitivity and β-cell function, and to what extent these associations are explained by skeletal muscle mass relative to body size. In addition, further studies should investigate whether the effects of strength and fitness in adolescence persist in adulthood despite changes in these physical fitness characteristics in adulthood.

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A.G. researched data and wrote the manuscript. M.R.-L. researched data and reviewed and edited the manuscript. U.E. contributed to discussion and reviewed and edited the manuscript. K.F. researched data and contributed discussion. S.B. contributed to discussion and reviewed and edited the manuscript. L.B.A. researched data, contributed discussion, and reviewed and edited the manuscript. A.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus—present and future perspectives. Nat Rev Endocrinol 2012;8:228–236
2. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care 2011;34:1249–1257
3. Li C, Ford ES, Zhao G, Mokdad AH. Prevalence of pre-diabetes and its association with clustering of cardiometabolic risk factors and hyperinsulinemia among U.S. adolescents: National Health and Nutrition Examination Survey 2005-2006. Diabetes Care 2009;32:342–347
4. Franks PW, Hanson RL, Knowler WC, Sievers ML, Bennett PH, Looker HC. Childhood obesity, other cardiovascular risk factors, and premature death. N Engl J Med 2010;362:485–493
5. Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. JAMA 2006;296:421–426
6. Carnethon MR, Sternfeld B, Schreiner PJ, et al. Association of 20-year changes in cardiorespiratory fitness with incident type 2 diabetes: the coronary artery risk development in young adults (CARDIA) fitness study. Diabetes Care 2009;32:1284–1288
7. Sui X, Jackson AS, Church TS, et al. Effects of cardiorespiratory fitness on aging: glucose trajectory in a cohort of healthy men. Ann Epidemiol 2012;22:617–622
8. Dwyer T, Magnussen CG, Schmidt MD, et al. Decline in physical fitness from childhood to adulthood associated with increased obesity and insulin resistance in adults. Diabetes Care 2009;32:683–687
9. Riddoch C, Edwards D, Page A, et al. The European Youth Heart Study-cardiovascular disease risk factors in children: rationale, aims, design and validation of methods. J Phys Act Health 2005;2:115–129
10. Andersen LB, Henckel P. Maximal voluntary isometric strength in Danish adolescents 16-19 years of age. Eur J Appl Physiol Occup Physiol 1987;56:83–89
11. Essendrop M, Schibye B, Hansen K. Reliability of isometric muscle strength tests for the trunk, hands and shoulders. Int J Ind Ergon 2001;28:379–387
12. Kolle E, Steene-Johannessen J, Andersen LB, Anderssen SA. Objectively assessed physical activity and aerobic fitness in a population-based sample of Norwegian 9- and 15-year-olds. Scand J Med Sci Sports 2010;20:e41–e47
13. Anderssen SA, Cooper AR, Riddoch C, et al. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. Eur J Cardiovasc Prev Rehabil 2007;14:526–531
14. Grøntved A, Ried-Larsen M, Møller NC, et al. Youth screen-time behaviour is associated with cardiovascular risk in young adulthood: the European Youth Heart Study. Eur J Prev Cardiol Jul 5 [Epub ahead of print]
15. Kristensen PL, Moeller NC, Korsholm L, et al. The association between aerobic fitness and physical activity in children and adolescents: the European youth heart study. Eur J Appl Physiol 2010;110:267–275
16. Ekelund U, Brage S, Froberg K, et al. TV viewing and physical activity are independently associated with metabolic risk in children: the European Youth Heart Study. PLoS Med 2006;3:e488
17. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419
18. Gungor N, Saad R, Janosky J, Arslanian S. Validation of surrogate estimates of insulin sensitivity and insulin secretion in children and adolescents. J Pediatr 2004;144:47–55
19. Balkau B, Charles MA. Comment on the provisional report from the WHO consultation. European Group for the Study of Insulin Resistance (EGIR). Diabetic Med 1999;16:442-443.
20. Royston P. Multiple imputation of missing values. Stata J 2004;4:227–241
21. *Physical Activity Guidelines Advisory Committee Report*. Washington, DC, US Department of Health and Human Services, 2008. Available from http://www.health.gov/paguidelines/guidelines/default.aspx. Accessed 28 October 2012
22. World Health Organization. *Global Recommendations on Physical Activity for Health*. Geneva, Switzerland, WHO Press, 2010
23. Shaibi GQ, Cruz ML, Ball GD, et al. Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. Med Sci Sports Exerc 2006;38:1208–1215
24. Benson AC, Torode ME, Fiatarone Singh MA. The effect of high-intensity progressive

resistance training on adiposity in children: a randomized controlled trial. Int J Obes 2008;32(6):1016–1027
25. Lee S, Bacha F, Hannon T, Kuk JL, Boesch C, Arslanian S. Effects of aerobic versus resistance exercise without caloric restriction on abdominal fat, intrahepatic lipid, and insulin sensitivity in obese adolescent boys: a randomized, controlled trial. Diabetes 2012;61:2787–2795
26. Behm DG, Faigenbaum AD, Falk B, Klentrou P. Canadian Society for Exercise Physiology position paper: resistance training in children and adolescents. Appl Physiol Nutr Metab 2008;33:547–561
27. Steene-Johannessen J, Anderssen SA, Kolle E, Andersen LB. Low muscle fitness is associated with metabolic risk in youth. Med Sci Sports Exerc 2009;41:1361–1367
28. Artero EG, Ruiz JR, Ortega FB, et al.; HELENA Study Group. Muscular and cardiorespiratory fitness are independently associated with metabolic risk in adolescents: the HELENA study. Pediatr Diabetes 2011;12:704–712
29. Benson AC, Torode ME, Singh MA. Muscular strength and cardiorespiratory fitness is associated with higher insulin sensitivity in children and adolescents. Int J Pediatr Obes 2006;1:222-231.
30. Sigal RJ, Kenny GP, Boulé NG, et al. Effects of aerobic training, resistance training, or both on glycemic control in type 2 diabetes: a randomized trial. Ann Intern Med 2007;147:357–369
31. Church TS, Blair SN, Cocreham S, et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: a randomized controlled trial. JAMA 2010;304:2253–2262
32. van Dijk JW, Manders R, Tummers K, et al. Both resistance- and endurance-type exercise reduce the prevalence of hyperglycaemia in individuals with impaired glucose tolerance and in insulin-treated and non-insulin-treated type 2 diabetic patients. Diabetologia 2012;55:1273–1282
33. Grøntved A, Rimm EB, Willett WC, Andersen LB, Hu FB. A prospective study of weight training and risk of type 2 diabetes mellitus in men. Arch Intern Med 2012;172:1306–1312
34. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495

Supplementary Table 1. Isometric muscle strength and cardiorespiratory fitness in youth and fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood. Results are from the imputed analyses of the total sampled population at baseline (n=873) using chained equations ("mi impute" in STATA). All covariates and respective outomes were included in the imputation approach. Beta coefficients and SE's were based on 20 imputed datasets.

	Beta (95% CI)	P
Muscle strength		
Glucose[a]	-0.02 (-0.11;0.06)	0.58
Insulin[b]	-10.9 (-16.5;-5.0)	0.001
HOMA-IR[b]	-11.6 (-17.5;-5.4)	0.001
HOMA-B[b]	-9.6 (-15.9;-2.9)	0.007
Cardiorespiratory fitness		
Glucose[a]	-0.02 (-0.09;0.05)	0.50
Insulin[b]	-11.3 (-18.6;-3.3)	0.008
HOMA-IR[b]	-11.6 (-17.3;-5.6)	<0.001
HOMA-B[b]	-10.4 (-16.0;-4.3)	0.001

[a]Beta coefficient (95% CI) represents mmol/l change in glucose in young adulthood per each 1 SD difference in muscle strength or cardiorespiratory fitness in adolescence.

[b]Beta coefficient (95% CI) represents change in ratios of geometric means (expressed in percentage) in insulin, HOMA-IR or HOMA-B in young adulthood per each 1 SD difference in muscle strength or cardiorespiratory fitness in adolescence.

Models were adjusted for baseline levels of risk factor, age at baseline, age at follow-up, gender, recruitment period, TV-viewing, parental education level, smoking status, intake of soft drinks, fruit- and vegetable intake, family history of diabetes. Models included both muscle strength and cardiorespiratory fitness (mutually adjusted).

Supplementary Table 2. Separate associations of isometric abdominal- and back muscle strength in youth with fasting glucose, insulin, HOMA-IR, and HOMA-B in young adulthood.

	Beta (95% CI)	P
Abdominal muscle strength		
Glucose[a]	-0.01 (-0.07;0.04)	0.67
Insulin[b]	-9.6 (-15.6;-3.1)	0.004
HOMA-IR[b]	-10.2 (-16.6;-3.3)	0.005
HOMA-B[b]	-7.9 (-13.7;-1.8)	0.01
Back muscle strength		
Glucose[a]	-0.03 (-0.08;0.02)	0.29
Insulin[b]	-10.3 (-15.5;-4.5)	0.001
HOMA-IR[b]	-11.3 (-17.0;-5.1)	0.001
HOMA-B[b]	-7.7 (-12.9;-2.1)	0.01

[a]Beta coefficient (95% CI) represents mmol/l change in glucose in young adulthood per each 1 SD difference in muscle strength in adolescence.

[b]Beta coefficient (95% CI) represents change in ratios of geometric means (expressed in percentage) in insulin, HOMA-IR or HOMA-B in young adulthood per each 1 SD difference in muscle strength in adolescence.

All models were adjusted for baseline levels of the outcome, age, gender, recruitment period, TV-viewing, parental education level, smoking status, intake of soft drinks, fruit- and vegetable intake, family history of diabetes, and cardiorespiratory fitness.

Paper VI

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Title

Screen time viewing behaviors and isometric trunk muscle strength in youth

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Running title: Screen time viewing and trunk muscle strength

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Abstract

Purpose

To examine the association of screen time viewing behavior with isometric trunk muscle strength in youth.

Methods

A cross-sectional study was carried out including 606 adolescents (14-16-years old) participating in the Danish European Youth Heart Study; a population-based study with assessments conducted in either 1997/98 or 2003/04. Maximal voluntary contractions during isometric back extension and abdominal flexion were determined using a strain-gauge dynamometer, and cardiorespiratory fitness (CRF) was obtained using a maximal cycle ergometer test. Television (TV) viewing time, computer use, and other lifestyle behaviors were obtained by self-report. Analyses of association of screen use behaviors with isometric trunk muscle strength were carried out using multivariable adjusted linear regression.

Results

Mean (SD) isometric strength was 0.87 (0.16) N/kg. TV viewing, computer use, and total screen time use were inversely associated with isometric trunk muscle strength in analyses adjusted for lifestyle and socio-demographic factors. After further adjustment for CRF and waist circumference, associations remained significant for computer use and total screen time but TV viewing were only marginally associated with muscle strength after these additional adjustments (-0.05 (95%CI -0.11;0.005) SD difference in strength per 1 hours/day difference in TV viewing time, p=0.08). Each 1 hour/day difference in total screen time use was associated with -0.09 SD (95%CI -0.14;-0.04) lower isometric trunk muscle strength in the fully adjusted model (p=0.001). There were no indications that the association of screen time use with isometric trunk muscle strength was attenuated among highly fit individuals (p=0.91 for CRF by screen time interaction).

Conclusions

Screen time use was inversely associated with isometric trunk muscle strength independent of CRF and other confounding factors.

Keywords: Fitness, television, computer, adolescents, sedentary

Introduction

Television (TV) viewing and computer use - two very common sedentary behaviors among youth - are usually performed in a seated or lying posture for longer periods of time. The number of daily switches between seated/lying and standing/walking positions is likely to be affected by excessive time spent on these viewing behaviors. Thus, besides displacing time spent on physical activity, excessive screen time use may also influence posture allocation, which could explain part of the adverse health effects of screen time viewing reported on outcomes such as type 2 diabetes, cardiovascular diseases, premature mortality, and its biological risk factors (5, 8, 9, 26). A number of previous studies have shown that prolonged screen time viewing in childhood or youth may lead to poorer cardiorespiratory fitness (CRF) later in life independent of the level of physical activity and other determinants of CRF (12, 20). However, time spent in the seated or lying posture, a reduced number of posture transitions, and less time spent on physical activity as a result of excessive viewing time could also influence muscle strength, in particular trunk muscle strength. To further explore whether screen time viewing behaviors influence trunk muscle strength, we examined the association of screen time behaviors with abdominal and back isometric strength in a population sample of Danish youth with adjustment for potential confounding factors such as CRF.

Methods

Design

This study was cross-sectional and used data from the Danish EYHS, an international population-based multicenter study that addresses cardiovascular disease (CVD) risk factors in children and adolescents (23). For this particular investigation, the eligible participants were 429 adolescents from the assessment wave in 1997-98, and 444 adolescents from the 2003-04 wave. In 1997-98, a sub-group of 243 participants had isometric muscle strength assessed, and in 2003-04 n=441 had isometric muscle strength evaluated. The local scientific ethics committee approved the study and all participants gave informed consent to participate.

Television, computer use, and total screen time viewing

TV viewing and computer use during leisure was obtained by self-report using a computer-based questionnaire (9). Two questions were asked about the amount of time viewing TV (before and after school). From these two questions a summary variable of daily TV viewing time variable was constructed (hours/day). Daily time spent using computer was asked in one question. A total screen time variable (hours/day) was created by summarizing TV and computer use.

Muscle strength

Isometric muscle strength was obtained during maximal voluntary contraction (MVC) of abdominal and back muscles using a strain-gauge dynamometer (1). The participants were standing upright

and positioned with a strap around the shoulders connected to the dynamometer. Abdominal MVC was performed with the back against the dynamometer performing maximal forward flexion. For MVC of the lower back muscles, the participants were positioned with the front against the dynamometer performing maximal backward extension. We expressed total isometric trunk muscle strength (Newton (N)) as the mean of abdominal- and back strength relative to body weight (in N/kg). Previous studies have reported a high reliability of these particular isometric strength measures in adults (intraclass correlation coefficient>0.9) (6).

Cardiorespiratory fitness

We assessed CRF during a progressive maximal ergometer bicycle test (Ergomedic 839; Monark, Varberg, Sweden) (23). Heart rate (HR) was recorded every 5 s during the test using a HR monitor (Polar Vantage, Finland). Criteria for a maximal effort were HR of 185 beats per minute or greater, and a subjective judgment by the observer that the participant could no longer continue, even after verbal encouragement. Maximal power output (wattmax) was used to estimate maximal oxygen uptake using the following equation VO_2-max (ml O_2/min/kg) = 0.465+(0.0112*wattmax)+(0.172*gender) / kg body weight, where gender is boys=1 and girls=0 (15). The fitness measure is highly reproducible (coefficient of variation 2.5-4.8%) and a previous validation study among 15-year olds have shown that this measure is highly correlated with directly measured VO_2-max (r>0.90, P<0.001) (2).

Other covariates

Height and weight were measured while the participants were wearing light clothing, without shoes, using standard anthropometric procedures. Waist circumference (WC) was measured to the nearest 1 mm at the midpoint between the lower ribs and the iliac crest with a flexible tape. Smoking status (yes/no), monthly frequency soft drinks, fruit, and vegetable intake were obtained by self-report in adolescence using a computer-based questionnaire as describes previously (23). Parental educational level was obtained by parental self-report. Parental educational status was defined according to the International Standard Classification of Education (ISCED) (UNESCO 1997). However, as the details obtained of the description of education were insufficient, the ISCED seven-point scale was combined into 3 new groups (I=level 1-2; II=level 3-4; and III=level 5-7). Moderate and vigorous physical activity (MVPA) was assessed using accelerometry with data reduction as described previously (18). Specifically, an accelerometer output >2000 counts/min (equivalent to walking about 4 km/h) was defined as MVPA and expressed as percentage of total registered time.

Statistics

Associations of TV viewing, computer use, and total screen time use with isometric trunk muscle strength (standardized score (SD)) was analyzed using multivariable adjusted linear regression.

Initially, we ran models adjusting for age, sex, recruitment wave, parental educational status, smoking status, intake of soft drinks, and fruit- and vegetable intake. We then ran analyses with additional adjustment for CRF and waist circumference. We also ran a multivariable adjusted model including both TV viewing and computer use in the same model to assess whether both types of screen-based behavior were associated with isometric trunk muscle strength, independent of each other.

We also examined the association of screen time use with isometric trunk muscle strength by CRF level, parental educational level, and sex. Interaction between screen time and these factors were examined by including interaction terms with main effects included in the multivariable models.

In sensitivity analyses, we additionally adjusted for accelerometry-measured MVPA to examine if any residual confounding by physical activity remained that CRF may not have captured. Because 37% of the participants with otherwise full data had missing information on accelerometer measured MVPA, we imputed missing values on MVPA using a multiple linear regression imputation approach ("mi impute" in STATA) including all covariates and the outcome. We obtained beta coefficients and standard errors (SE) based on 20 imputed datasets while the variability between imputations is adjusted for (24).

All statistical analyses were performed in STATA 12.1 with alpha=0.05 (two-sided).

Results

The present study included a total of 606 14-16 year old adolescents of whom 205 were recruited in 1997/98 and 401 in 2003/04. Table 1 shows selected characteristics of the included participants in the present study compared with participants excluded due to missing data (n=267). There were no difference between included participants and individuals with missing data in majority of characteristics, except for age, gender, and TV viewing time. Individuals with missing data were slightly older, viewed more TV and the percentage of boys compared to girls was lower (Table 1). The mean screen time was 2.8 hours/day among boys and 1.8 hours/day among girls participating in the study. The Spearman correlation coefficient between TV viewing and computer use was 0.10 (p=0.02).

The associations of television viewing, computer use, and total screen time with isometric trunk muscle strength in youth are shown in Table 2. In basic multivariable adjusted models without adjustment for CRF and waist circumference, all screen time behaviors were significantly associated with abdominal-, back-, and total isometric trunk muscle strength. After further adjustment for fitness and waist circumference, associations of computer use and total screen time use were moderately attenuated but were still associated with both abdominal, back, and total isometric trunk muscle strength ($p<0.05$). Each 1 hour/day difference in total screen time was associated with -0.09 (95%CI -0.14;-0.04) SD difference in isometric trunk muscle strength in fully adjusted analysis. TV viewing was marginally associated with total isometric trunk

muscle strength in fully adjusted models (-0.05 (95%CI -0.11;0.005) SD difference in strength per 1 hours/day difference in viewing time, p=0.08). There was no indications that screen time was non-linearly associated with isometric trunk muscle strength, either based on visual inspection (Figure 1) or based on statistical evaluation by including a quadratic term of total screen time in the fully adjusted multivariable model (p=0.12). Results were unaltered when adjusting the analyses for waist-to-height ratio or BMI instead of waist circumference (data not shown). Additional adjustment for accelerometer measured MVPA did not alter the associations; each 1 hour/day difference in total screen time was associated with -0.08 (95%CI -0.13;-0.03) SD difference in isometric trunk muscle strength in fully adjusted analysis including waist circumference and CRF. When we included TV viewing and computer use in the model, the estimates of association with isometric trunk muscle strength was close to similar compared with the analyses of each viewing type analyzed separately ($beta_{computer}$=-0.18 (95%CI -0.27;-0.08) SD, $beta_{TV}$=-0.05 (95%CI -0.11;0.008) SD, p=0.09). We also examined if isometric trunk muscle strength was different according to achievement of youth recommendations for screen time (≤2 hours/day). Adolescents not exceeding the recommended levels for screen time (4, 27) had -0.18 (95%CI -0.32;-0.04) SD difference in isometric trunk muscle strength, compared with adolescents achieving recommendations (p=0.01).

We also analyzed the association of screen time with CRF adjusting for the same covariates including total isometric trunk muscle strength and waist circumference. Each 1 hour/day difference in total screen time was associated with -0.04 (95%CI -0.08;-0.01) SD difference in CRF in this analysis (p=0.02).

We then ran analyses of the association of total screen time with total isometric trunk muscle strength stratified by sex-specific quartiles of CRF, parental educational level, and sex (Figure 2). In these analyses, we did not see statistical evidence of interaction between these factors and screen time (p>0.3 for all interactions).

Discussion

In this cross-sectional study of a population sample of Danish youth excessive screen time behaviors were associated with lower isometric trunk muscle strength. Importantly, these inverse associations were independent of CRF, general or abdominal adiposity, and other lifestyle- and socio-demographic factors. Furthermore, we did not see any indication that the association of screen time use with muscle strength was attenuated among high-fit individuals, which suggests that limiting screen time use could be beneficial for improving or maintaining isometric trunk muscle strength even among cardiorespiratory fit individuals. Because daily excessive time spent in a seated or lying position is likely to reduce exposure to postures requiring greater muscle tone and potentially also posture transitions, this could explain these inverse associations. We adjusted our analyses for CRF to capture current- and long-term engagement in physical activity, which undoubtedly is an important confounder in the relation of screen time exposure with muscle

strength. We cannot rule out that residual confounding remain for CRF and physical activity as excessive computer use and TV viewing are associated with other unhealthy behaviors including concomitant intake of unhealthy foods, as well as TV advertisements and TV/computer content may influence other unhealthy behaviors. Thus, it could be that the inverse associations of these viewing behaviors with isometric trunk muscle strength are explained by factors, which we have not fully adjusted for.

We are aware of only one other study examining the association of screen time and isometric trunk muscle strength. Our study is in agreement with a cross sectional study among Finnish young adults that reported an inverse association of TV viewing with isometric trunk muscle strength assessed using similar procedures (21). These associations were reported being independent of self-reported "brisk" physical activity and smoking status but were not adjusted for CRF and other lifestyle- and socio-demographic factors. Furthermore, the evaluation did not include computer use nor make sequential adjustment for adiposity, so it is not unlikely that reported associations have a larger degree of confounding by adiposity and other unmeasured factors associated with young adult lifestyle. The observations from our study are also supported by findings from a prospective study of Canadian toddlers followed until 2nd grade (7). In that study, increases in parentally reported TV viewing time between the age of 2.5 and 4.5 years predicted shorter long jump performance at 8 years of age independent of parentally reported physical activity, and other characteristics including child weight status at follow-up. Finally, two cross-sectional studies carried out in the 1970s and early 1980s have reported inverse associations of TV viewing time with components of muscle strength and fitness (14, 28).

We are not aware of randomized trials examining the effect of reducing any type of sedentary behavior including screen-based behaviors on muscle strength. However, a small scale randomized trial have examined the effect of changing school furniture to adjustable desks and chairs with sitting trunk–thigh angle adjusted to 135° compared with traditional school desks and chairs with sitting trunk–thigh angle of 90° for a period of 2 years among high school student. This study found that the intervention increased abdominal- and back muscle strength (16). These results supports the notion that specific postures while sitting are important for development or maintaining of trunk muscle strength. We have previously reported that low isometric MVC of the trunk and prolonged screen time use in youth are associated with greater adiposity, insulin resistance, and raised levels of other cardiovascular risk factors in young adulthood independent of CRF (10, 11). Thus, limiting screen time use or introducing more standing while engaging in screen time could be important targets for maintaining isometric trunk muscle strength and subsequently in preventive measures against development of insulin resistance and other metabolic abnormalities later in life. Clearly more evidence from experimental studies is needed on this topic to infer, with greater confidence, that these associations are causal and to test the effectiveness of interventions such as standing desks on physical fitness and other health outcomes.

The major strength of the study was that we were able to adjust our analyses for a range of important confounding factors including CRF. Furthermore, we assessed isometric trunk muscle strength using a highly reliable method. We were also able to examine both TV viewing time and computer use separately, which are two analogues behaviors in the sense that both behaviors are usually performed seated or in a lying position and likely to reduce exposure to posture requiring greater muscle tone. Since associations with isometric trunk muscle strength for both type of viewing behavior were unaffected by mutual adjustment, this strengthens the inference that posture allocation or sitting/lying time explains the associations. Besides the possibility that residual and unknown confounding could explain the results, there are some additional limitations to the study. The inverse associations of screen time use and muscle strength could also be a result of reverse-causality, i.e. screen time use increases as a result of poor strength. As our study was cross sectional we could not tease out the extent of this possible reverse causation bias. Although we did not see a sex-by-screen time use interaction on muscle strength, sex stratified analyses indicated that associations were less strong for girls and larger studies are needed to further examine this. Furthermore, the assessments of screen time viewing behaviors were based on self-report, and we cannot rule out the possibility of recall bias (i.e. that screen time use is over- or underestimated dependent on the level of isometric trunk muscle strength). Reliability of self-reported screen use among adolescents has been reported moderate to excellent (3, 13, 22, 25, 29), and validity against diary as the criterion measure has been reported moderate (25, 29). We did not analyze associations of accelerometer measured sedentary time or breaks in sedentary time with isometric trunk muscle strength. While accelerometers worn on the hip are commonly used to objectively assess physical activity based on a large pool of extensive validation studies, a hip-mounted accelerometer is less suitable to assess activity in the lower spectrum of the activity continuum (sedentary behavior) and can only poorly distinguish between sitting and standing or characterize breaks in sitting time (17, 19). Furthermore, the use of accelerometry in the assessment of sedentary time and components of sedentary time such as breaks have not been rigorously evaluated with respect to impact of data reduction choices and participants adherence to monitoring protocol on error in estimation of sedentary time in association analyses with health outcomes. In addition, while the isometric muscle strength assessment procedures are very reliable in adults, we did not evaluate reliability of the tests in youth, which remains to be determined.

In summary, in a population sample of Danish youth screen time use was inversely associated with isometric trunk muscle strength independent of CRF, lifestyle behaviors, adiposity, and socio-demographic factors. Further studies are needed to disentangle whether the prolonged time spent in a seated or lying position and possibly fewer posture allocations are driving this association, which would therefore be important behavioral intervention targets for maintaining trunk muscle strength.

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References

1. Andersen LB, Henckel P. Maximal voluntary isometric strength in Danish adolescents 16-19 years of age. *Eur J Appl Physiol Occup Physiol*. 1987;56(1):83-9.
2. Anderssen SA, Cooper AR, Riddoch C et al. Low cardiorespiratory fitness is a strong predictor for clustering of cardiovascular disease risk factors in children independent of country, age and sex. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2007;14(4):526-31.
3. Atkin AJ, Gorely T, Clemes SA et al. Methods of Measurement in epidemiology: Sedentary Behaviour. *International Journal of Epidemiology*. 2012;41(5):1460-71.
4. Committee on Public Education. Children, Adolescents, and Television. *Pediatrics*. 2001;107(2):423-6.
5. Dunstan DW, Kingwell BA, Larsen R et al. Breaking Up Prolonged Sitting Reduces Postprandial Glucose and Insulin Responses. *Diabetes Care*. 2012;35(5):976-83.
6. Essendrop M, Schibye B, Hansen K. Reliability of isometric muscle strength tests for the trunk, hands and shoulders. *International Journal of Industrial Ergonomics*. 2001;28(6):379-87.
7. Fitzpatrick C, Pagani LS, Barnett TA. Early childhood television viewing predicts explosive leg strength and waist circumference by middle childhood. *Int J Behav Nutr Phys Act.* 2012;9(1):87.
8. Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: A meta-analysis. *JAMA: The Journal of the American Medical Association*. 2011;305(23):2448-55.
9. Grøntved A, Ried-Larsen M, Møller NC et al. Youth screen time behaviour is associated with cardiovascular risk in young adulthood (The European Youth Heart Study). *European Journal of Preventive Cardiology*. 2012;(in press).
10. Grøntved A, Ried-Larsen M, Ekelund U, Froberg K, Brage S, Andersen LB. Independent and combined association of muscle strength and cardiorespiratory fitness in youth with insulin resistance and beta-cell function in young adulthood (The European Youth Heart Study). *Diabetes Care.* 2013 (in press)
11. Grøntved A, Ried-Larsen M, Møller NC, Kristensen PL, Froberg K, Brage S, Andersen LB. Muscle strength in youth and cardiovascular risk in young adulthood (The European Youth Heart Study). *British Journal of Sports Medicine.* 2013 (in press)

12. Hancox RJ, Milne BJ, Poulton R. Association between child and adolescent television viewing and adult health: a longitudinal birth cohort study. *The Lancet*. 2004;364(9430):257-62.
13. Hardy LL, Booth ML, Okely AD. The reliability of the Adolescent Sedentary Activity Questionnaire (ASAQ). *Preventive Medicine*. 2007;45(1):71-4.
14. Katzmarzyk PT, Malina RM, Song TMK, Bouchard C. Television viewing, physical activity, and health-related fitness of youth in the Québec family study. *Journal of Adolescent Health*. 1998;23(5):318-25.
15. Kolle E, Steene-Johannessen J, Andersen LB, Anderssen SA. Objectively assessed physical activity and aerobic fitness in a population-based sample of Norwegian 9- and 15-year-olds. *Scandinavian Journal of Medicine & Science in Sports*. 2010;20(1):e41-e7.
16. Koskelo R, Vuorikari K, Hänninen O. Sitting and standing postures are corrected by adjustable furniture with lowered muscle tension in high-school students. *Ergonomics*. 2007;50(10):1643-56.
17. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc.* Aug 2011;43(8):1561-156.
18. Kristensen P, Moeller N, Korsholm L et al. The association between aerobic fitness and physical activity in children and adolescents: the European youth heart study. *European Journal of Applied Physiology*. 2010;110(2):267-75.
19. Lyden K, Kozey Keadle SL, Staudenmayer JW, Freedson PS. Validity of two wearable monitors to estimate breaks from sedentary time. *Med Sci Sports Exerc.* 2012;44(11):2243-2252.
20. Mitchell JA, Pate RR, Blair SN. Screen-Based Sedentary Behavior and Cardiorespiratory Fitness from Age 11 To 13. *Med Sci Sports Exerc.* 2012;(1530-0315 (Electronic)).
21. Paalanne NP, Korpelainen RI, Taimela SP et al. Muscular fitness in relation to physical activity and television viewing among young adults. *Med Sci Sports Exerc.* 2009;41(11):1997-2002.
22. Rey-López JP, Ruiz JR, Ortega FB et al. Reliability and validity of a screen time-based sedentary behaviour questionnaire for adolescents: The HELENA study. *The European Journal of Public Health*. 2012;22(3):373-7.
23. Riddoch C, Edwards D, Page A et al. The European Youth Heart Study - cardiovascular disease risk factors in children: rationale, aims, design and validation of methods. *J Physical Activity Health*. 2005;2:115-29.
24. Rubin DB. Multiple Imputation After 18+ Years. *Journal of the American Statistical Association*. 1996;91(434):473-89.
25. Schmitz KH, Harnack L, Jacobs Jr DR et al. Reliability and Validity of a Brief Questionnaire to Assess Television Viewing and Computer Use. *Journal of School Health*. 2004;74(9):370-7.

26. Stamatakis E, Hamer M, Dunstan DW. Screen-Based Entertainment Time, All-Cause Mortality, and Cardiovascular Events: Population-Based Study With Ongoing Mortality and Hospital Events Follow-Up. *Journal of the American College of Cardiology*. 2011;57(3):292-9.
27. Tremblay MS, LeBlanc AG, Janssen I et al. Canadian Sedentary Behaviour Guidelines for Children and Youth. *Applied Physiology, Nutrition, and Metabolism*. 2011;36(1):59-64.
28. Tucker LA. The relationship of television viewing to physical fitness and obesity. *Adolescence*. 1986;21(84):797-806.
29. Vereecken CA, Todd J, Roberts C, Mulvihill C, Maes L. Television viewing behaviour and associations with food habits in different countries. *Public Health Nutrition*. 2006;9(02):244-50.

Table 1. Characteristics of the study population by gender and attrition analyses.

	Boys (n=292)	**Girls (n=314)**	**Total participants (n=606)**	**Individuals with missing data (n=200-267)**	P*
Characteristics					
Sex (% boys)	-	-	48.2	40.1 (n=267)	<0.01
Age (years)	15.6 (0.4)	15.6 (0.4)	15.6 (0.4)	15.7 (0.4) (n=267)	<0.01
BMI (kg/m^2)	21.0 (2.7)	21.1 (2.9)	21.0 (2.8)	21.0 (2.9) (n=267)	0.51
Waist circumference (cm)	74.5 (7.7)	71.1 (6.7)	72.8 (7.4)	70.0 (6.9) (n=266)	0.59
Abdominal strength (N/kg)	0.91 (0.18)	0.71 (0.14)	-	-	-
Back strength (N/kg)	0.98 (0.17)	0.88 (0.17)	-	-	-
Cardiorespiratory fitness (ml O_2/min/kg)	50.3 (6.8)	41.7 (5.6)	45.8 (7.5)	46.2 (8.2) (n=200)	0.10
Television viewing (hours/day)	1.8 (1.2)	1.5 (1.1)	1.6 (1.1)	1.8 (1.2) (n=255)	0.02
Computer use (hours/day)	1.1 (0.8)	0.3 (0.5)	0.6 (0.8)	0.5 (0.6) (n=255)	0.17
Soft drinks intake (servings/month)	13.1 (9.6)	7.4 (7.8)	10.1 (9.1)	10.9 (9.3) (n=255)	0.65
Fruit and vegetable intake (servings/month)	33.3 (17.4)	42.4 (16.6)	38.0 (17.6)	37.0 (16.8) (n=255)	0.64
MVPA (% of total time)	6.1 (3.1) (n=172)	4.8 (2.6) (n=207)	5.4 (2.9) (n=379)	5.1 (3.1) (n=131)	0.36
Parental education level (% 1 / 2 / 3)**	12.7 / 32.2 / 55.1	10.8 / 28.0 / 61.2	11.7 / 30.0 / 58.3	14.7 / 31.2 / 54.1 (n=231)	0.49
Smoking status (%)	22.6	17.5	20.1	27.5 (n=255)	0.17

Data are means (SD) or numbers (%). N=Newton, MVPA=moderate and vigorous physical activity.

*p-value for difference between participants and individuals with missing data adjusted for sex (except for analysis of sex-difference) and recruitment period.

**Based on educational level (International Standard Classification of Education (ISCED, UNESCO 1997), I=basic education; II=secondary or post-secondary education; and III=tertiary education).

Table 2. Association of television viewing, computer use, and total screen time viewing (hours/day) with isometric trunk muscle strength (SD) in youth.

	Model 1		Model 2		Model 3	
	Beta (95% CI)	p	Beta (95% CI)	p	Beta (95% CI)	p
Screen time variables						
			Abdominal muscle strength			
Television viewing (hours/day)	−0.09 (−0.15;−0.03)	0.004	−0.05 (−0.11;0.004)	0.07	−0.06 (−0.11;0.002)	0.06
Computer use (hours/day)	−0.20 (−0.30;−0.11)	<0.001	−0.19 (−0.28;−0.10)	<0.001	−0.19 (−0.29;−0.10)	<0.001
Total screen time use (hours/day)	−0.12 (−0.17;−0.07)	<0.001	−0.09 (−0.14;−0.04)	<0.001	−0.10 (−0.14;−0.04)	<0.001
			Back muscle strength			
Television viewing (hours/day)	−0.09 (−0.16;−0.02)	0.01	−0.04 (−0.10;0.03)	0.25	−0.04 (−0.10;0.02)	0.22
Computer use (hours/day)	−0.14 (−0.25;−0.03)	0.01	−0.12 (−0.22;−0.02)	0.02	−0.13 (−0.23;−0.03)	0.01
Total screen time use (hours/day)	−0.10 (−0.16;−0.04)	0.001	−0.06 (−0.11;−0.007)	0.03	−0.06 (−0.12;−0.01)	0.02
			Total trunk muscle strength			
Television viewing (hours/day)	−0.10 (−0.16;−0.03)	0.003	−0.05 (−0.11;−0.008)	0.09	−0.05 (−0.11; 0.005)	0.08
Computer use (hours/day)	−0.19 (−0.30;−0.09)	<0.001	−0.18 (−0.27;−0.08)	<0.001	−0.18 (−0.27;−0.08)	<0.001
Total screen time use (hours/day)	−0.12 (−0.17;−0.07)	<0.001	−0.08 (−0.13;−0.03)	0.001	−0.09 (−0.14;−0.04)	0.001

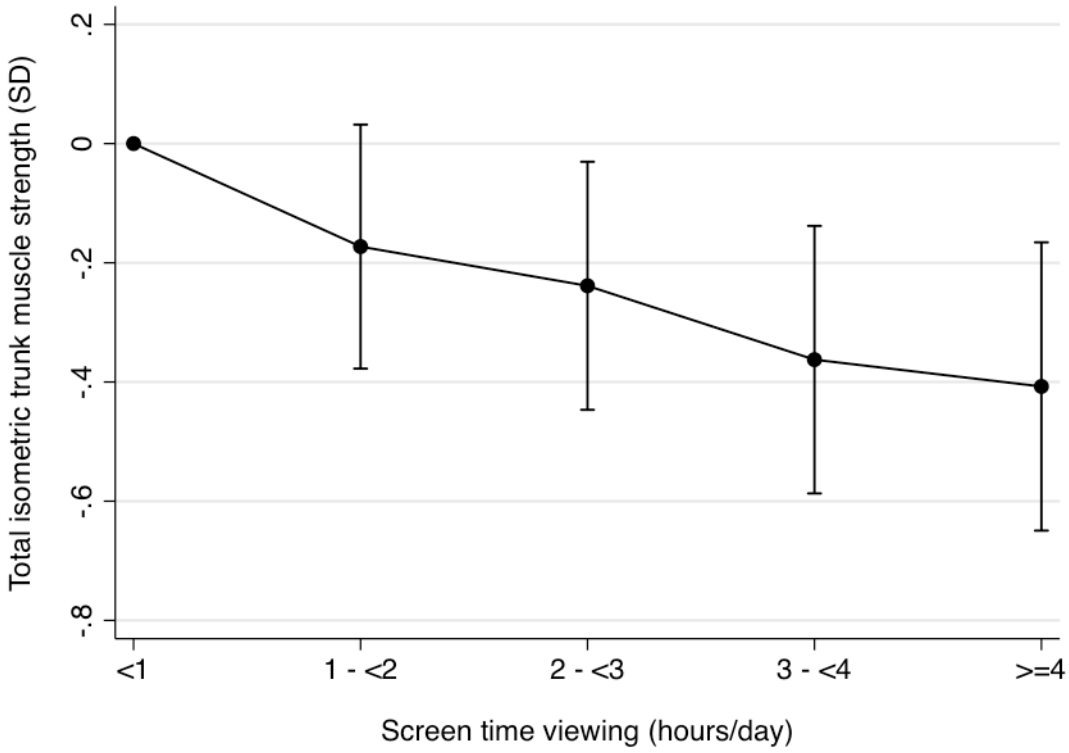
Beta coefficient (95% CI) represents change in youth isometric muscle strength (SD, 0.16 Newton/kg) per 1 hours/day difference in screen time viewing.

Model 1 was adjusted for age, sex, recruitment period, parental education level, smoking status, intake of soft drinks, fruit- and vegetable intake.

Model 2 was additionally adjusted for cardiorespiratory fitness.

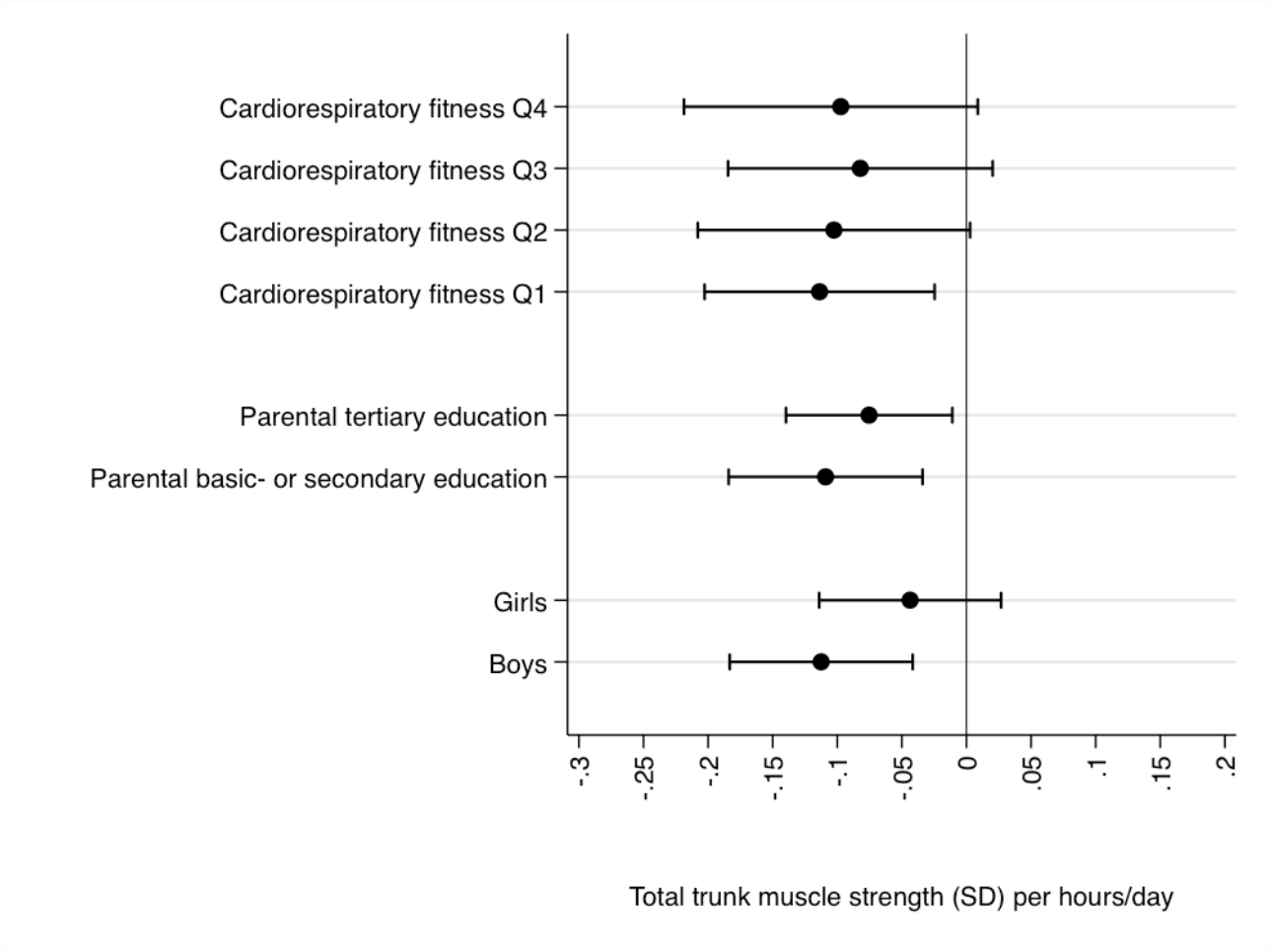
Model 3 was additionally adjusted for waist circumference.

Figure 1. Total isometric muscle strength (back and front trunk) against total screen time (TV viewing and computer use) in a population sample of Danish youth.



Estimates with 95% CI are from fully adjusted multiple regression analysis (as model 3 in Table 2).

Figure 2. Association of total screen time viewing (TV viewing and computer use, hours/day) with isometric trunk muscle strength (SD) in youth stratified by fitness (sex-specific quartiles), parental educational level (basic- or secondary education / tertiary education), and sex.



Estimates with 95% CI are from fully adjusted multiple regression analysis (as model 3 in Table 2). P=0.91 for fitness by screen time interaction, p=0.97 for educational level by screen time interaction, and p=0.36 for sex by screen time interaction on trunk muscle strength.