Influential Periods in Longitudinal Clinical Cardiovascular Health Scores

Amy E. Krefman, Darwin Labarthe, Philip Greenland, Lindsay Pool, Liliana Aguayo, Markus Juonala, Mika Kähönen, Terho Lehtimäki, R. Sue Day, Lydia Bazzano, Vito M.R. Muggeo, Linda Van Horn, Lei Liu, Larry S. Webber, Katja Pahkala, Tomi T. Laitinen, Olli Raitakari, Donald M Lloyd-Jones, and Norrina B. Allen

Correspondence to: Ms. Amy Krefman, MS, Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 N Lake Shore Drive, Suite 1400, Chicago, IL 60611. Phone: (312) 503-1432; Fax: (312) 908-9588; Email: amy.krefman@northwestern.edu

Author affiliations: Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois. (Amy E. Krefman, Darwin Labarthe, Philip Greenland, Lindsay Pool, Linda Van Horn, Donald M. Lloyd-Jones, and Norrina B. Allen); Rollins School of Public Health, Emory University, Atlanta, Georgia. (Liliana Aguayo); Department of Medicine, University of Turku, Finland and Division of Medicine, Turku University Hospital, Turku, Finland. (Markus Juonala); Department of Clinical Physiology, Tampere University Hospital and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland. (Mika Kähönen); Department of Clinical Chemistry, Finlab Laboratories and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland. (Terho Lehtimäki); Department of Epidemiology, The University of Texas Health Science Center at Houston (UTHealth) School of Public Health, Houston, Texas. (R. Sue Day); Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana. (Lydia Bazzano); Dip. Scienze Econ, Az e Statistiche, Università di Palermo, Italy. (Vito M.R. Muggeo); Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri. (Lei Liu); Emeritus Professor, Department of Global Biostatistics and Data Science, School of Public Health and Tropical Medicine, Tulane University, New Orleans, Louisiana. (Larry S. Webber); Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku. (Katja Pahkala, Tomi T. Laitinen, and Olli Raitakari); Paavo Nurmi Centre, Sports & Exercise Medicine Unit, Department of Health and Physical Activity, University of Turku, Turku, Finland. (Katja Pahkala and Tomi T. Laitinen); Centre for Population Health Research, University of Turku and Turku University Hospital. (Olli Raitakari); and Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland. (Olli Raitakari).

© The Author(s) 2021. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
Funding: This work was supported by an American Heart Association Strategically Funded Prevention Research Network Center Grant to Northwestern (AHA Award #14SFRN20780002).

The Young Finns Study has been financially supported by the Academy of Finland: grants 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117787 (Gendi), and 41071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gunnellberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS); European Research Council (grant 742927 for MULTIEPIGEN project); and Tampere University Hospital Supporting Foundation.

The BHS was supported by grants R01HL121230 from the National Heart, Lung and Blood Institute, ES021724 from National Institute of Environmental Health Sciences, R01AG016592 from National Institute of Aging, and P20GM109036 from the National Institute of General Medical Sciences of the National Institutes of Health.

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN2682018000051 & HHSN2682018000071), Northwestern University (HHSN2682018000031), University of Minnesota (HHSN2682018000061), and Kaiser Foundation Research Institute (HHSN2682018000041). This manuscript has been reviewed by CARDIA for scientific content.

STRIP has been supported by Academy of Finland (206374, 294834, 251360, 275595); Juho Vainio Foundation; Finnish Cultural Foundation; Finnish Foundation for Cardiovascular Research; Sigrid Jusélius Foundation; Yrjö Jahnsson Foundation; Finnish Diabetes Research Foundation; Novo Nordisk Foundation; Finnish Ministry of Education and Culture; Special Governmental Grants for Health Sciences Research, Turku University Hospital; and University of Turku Foundation.

Project HeartBeat! has been supported by the following research awards from NIH and the CDC: U01 HL41166; 1RO3 HL57101; 1RO3 HL59223 (cardiac development); and CDC contract PO# 000966385, Intergovernmental Personnel Agreement 00IPA24501, and Cooperative Agreement U48/CCU609653. Additional support from the Compaq Computer Corporation and the University of Texas Health Science Center at Houston, School of Public Health, is also gratefully acknowledged.

Running head: Influential Periods in Cardiovascular Health
Abstract:
The prevalence of ideal cardiovascular health (CVH) among adults in the United States is low, and decreases with age. Our objective was to identify specific age windows when the loss of CVH accelerates, to ascertain preventive opportunities for intervention. This study pools data from five longitudinal cohorts (Project Heartbeat!, Cardiovascular Risk in Young Finns Study, The Bogalusa Heart Study, Coronary Artery Risk Development in Young Adults (CARDIA), Special Turku Coronary Risk Factor Intervention Project (STRIP)) from the United States and Finland from 1973 to 2012. Individuals with clinical CVH factors (body mass index, blood pressure, cholesterol, blood glucose) measured between ages 8 to 55 were included. These factors were categorized and summed into a clinical CVH score ranging from 0 (worst) to 8 (best). Adjusted segmented linear mixed models were used to estimate the change in CVH over time. Among the 18,343 participants, 9461(52%) were female and 12,346(67%) White. The baseline mean (SD) clinical CVH score was 6.9(1.2) at an average age of 17.6(8.1). Two inflection points were estimated, at 16.9 years (95% CI: 16.4, 17.4) and at 37.2 years (95% CI: 32.4, 41.9). Late adolescence and early middle age appear to be influential periods at which the loss of CVH accelerates.

Keywords: adolescence, cardiovascular epidemiology, cardiovascular health, cohort studies, longitudinal studies, prevention, risk factors

Abbreviations: BMI, body mass index; BP, blood pressure; CARDIA, Coronary Artery Risk Development in Young Adults; CVH, cardiovascular health; STRIP, Special Turku Coronary Risk Factor Intervention Project; Young Finns, Cardiovascular Risk in Young Finns Study.
Heart disease remains the leading cause of death in the United States, and the current prevalence of ideal cardiovascular health (CVH) among adults in the United States is less than 5% (1,2). Ideal CVH is a concept, defined by the American Heart Association, and includes four health factors (body mass index (BMI), blood pressure (BP), total cholesterol, and fasting blood glucose) and three health behaviors (smoking, physical activity, and diet) (2). Ideal CVH has been linked to a broad range of improved health outcomes including greater longevity and quality of life; and lower risk for heart disease, incident cancer, and dementia (3). Ideal CVH prevalence decreases with age, but whether declines are consistent across the life course is unknown. Identifying if there are ages when the rate of CVH decline accelerates could facilitate better targeting of preventive efforts to these periods, as well as to further understand the causes and drivers of loss of CVH which may be due to specific developmental periods across the lifecourse.

Recent advances in estimation of change points allow us to estimate when decline in CVH begins to accelerate across the life course. Previous studies have looked at overall patterns or trajectories of CVH over time, to determine how the trajectories correspond to future risk and characterize which children may be more likely to be in specific risk categories, which has provided important information about risk stratification (4,5). This work expands on this concept by decomposing risk over time to determine specific periods or ages, which previous studies have not been able to quantitatively assess.

This study seeks to estimate influential age windows when the rate of decline in CVH changes at the population level, in order to identify opportunities to promote and maintain ideal CVH throughout the lifetime. In addition to identifying these influential change points, we wanted to
determine whether there are sex differences in the rate of change between change points, as well as how the individual metrics were changing over time. We hypothesize CVH declines are not consistent across the life course and there is at least one age when the rate of decline significantly changes.

METHODS

Cohorts and participants

This study included 18,343 individuals from five cohorts – Project Heartbeat! (6), Cardiovascular Risk in Young Finns Study (Young Finns) (7), The Bogalusa Heart Study (8), Coronary Artery Risk Development in Young Adults (CARDIA) (9), Special Turku Coronary Risk Factor Intervention Project (STRIP) (10). Details of harmonizing these cohorts’ data are described elsewhere (4). In brief, each cohort collected clinical measurements at in-person exams and used questionnaires to collect demographic and behavioral data over varied ages and lengths of time. By including cohorts that span overlapping age windows, we are able to cover a wider range, from 8 to 55 years. Participants were included in the analysis if they had at least one clinical CVH score (all four clinical CVH components measured at the same exam), described below (Web Figure 1). Parental education, categorized as years of education, was collected as a proxy for socioeconomic status.

CVH factors

CVH factors available from all studies included BMI, BP, lipids and fasting glucose. BMI was calculated from measured weight (in kilograms) and the square of the height (in meters). Prior to calculating CVH score, BMI was converted to an age- and sex-specific percentile for those under the age of 20 years using the Centers for Disease Control and Prevention (CDC) calculation (11).
Systolic and diastolic BP were measured in all cohorts at every exam. BP was converted to percentile values for those < 18 years using the pediatric hypertension guidelines published in 2017 (12).

Fasting serum lipids and fasting blood (plasma or serum) glucose levels were measured at multiple exams for each cohort.

Each BMI, BP, fasting glucose, and total cholesterol observation was considered ideal, intermediate, or poor based on American Heart Association criteria (Table 1) (2,4). To create a CVH score, points were assigned for the levels of each factor, zero for poor, one for intermediate, and two for ideal. Points from the four CVH factors measured at the same exam were summed to create a clinical CVH score. This score ranged from zero to eight, with higher levels of CVH score indicating better CVH. This score is associated with the future risk of heart disease – maintaining a higher score is associated with less risk (4).

CVH behaviors

CVH behaviors (smoking, diet, and physical activity), were not measured consistently across follow-up and thus were not included in the clinical CVH score. However, baseline behaviors were captured in each cohort, and were categorized as ideal or not ideal based on the American Heart Association criteria listed in Web Table 1 in order to describe the characteristics of the sample in Table 2 (2,13).

Statistical analysis

Demographic variables, CVH factors, CVH behaviors, and parental education measured at each participant’s baseline exam are described and stratified by sex (Table 2) and by age (Web Table 5).
We estimated the age at which distinct change points occurred in the mean clinical CVH score from age 8 through age 55 using piecewise linear regression extended to a longitudinal framework in the unpublished R function ‘segmented.lme’ (14). This approach allows for the estimation of interpretable parameters such as slopes and change points. First, the mixed model was fit with a random participant intercept and slope, and adjusted for race, sex, and cohort using ‘nlme’ in R (15). Next, we implemented an iterative procedure to estimate the change point(s) of the mixed model using ‘segmented.lme’. The change point(s) and their asymptotic 95% confidence intervals are estimated using a maximum likelihood approach. After the change point(s) were estimated, linear, quadratic, and cubic mixed models, and segmented linear mixed models with one and two change points were compared. The best fit was determined using AIC, BIC, and likelihood ratio tests (Web Table 2). As there was a significant interaction between age, race, and sex (P<0.001) in the initial mixed model, analyses were stratified by sex, and models were fit using the same procedure.

After estimating the change point(s), we tested the difference between the slopes in each age window (8 to <17 years, 17 to <37 years, and 37 to 55 years) by sex. The change in CVH score over time was modeled as a multivariable piecewise linear regression model with two knots (determined by the change point estimates described above), adjusting for race and cohort. Interaction terms between age and sex were included in the model to test for sex differences in the magnitude of change in CVH over time.

To further test the robustness of our models, we calculated means at age 8, 17, 37, and 55 years for each component of the CVH score separately (BMI, BP, fasting glucose and total cholesterol) using their original continuous values (for example, continuous systolic BP in mmHg rather than poor/intermediate/ideal BP). While age- and sex-specific percentiles were used to score BMI and
BP into ideal categories under age 20 (for BMI) and 18 (for BP), continuous metrics were used to calculate means for the purposes of continuity across the full age range. T-tests were used to determine if there was a significant difference between the means for males and females at each age.

Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina) and R version 3.3.3 (16) using the nlme package (15) and an extension of the segmented package written by Vito Muggeo for use with linear mixed models (14,17). Statistical significance was set a priori to \( P<0.05 \).

**RESULTS**

Among the 18,343 participants in our sample, 9461(52\%) were female and 12,346(67\%) were white. At the baseline exam, 10,463 (64\%) had ideal smoking status, while only 16\% had ideal diet or ideal physical activity scores. Mean age at baseline was 17.6(8.1) years. The mean (SD) clinical CVH score at baseline was 6.9(1.2) out of a possible 8.0 (Table 2).

In modeling clinical CVH scores over time, the adjusted segmented linear mixed model with two change points and random intercept and slope provided the best fit to the data compared to other models (Web Table 2). Change points in unadjusted models were estimated at 17.3 and 35.1 years (95\% confidence interval: 16.8, 17.8; 32.3, 37.9, respectively) as shown in Figure 1A. The adjusted model had change points at 16.9 (95\% confidence interval: 16.4, 17.4) and 37.2 years (95\% confidence interval: 32.5, 41.9). This second inflection point’s uncertainty, causing a somewhat wider confidence interval, reflected a much smaller acceleration in the rate of decline. Prior to the first change point in both the unadjusted and adjusted models, beginning from age 8 years in the present data, the rate of decline was close to zero (0.01 points per year, 95\%
confidence interval: -0.004, 0.02 in the adjusted model). After the first change point, the rate of decline significantly increased to -0.07 points per year (95% confidence interval: -0.08, -0.07). At that rate, an individual would lose 1.5 points in their clinical CVH score in the 20 year span between age 17 and 37. After age 37, the rate of decline increased further to -0.08 (95% confidence interval: -0.09, -0.08) points per year (Figure 2).

The stratified models determining change points for males and females did not differ significantly from each other, or the overall estimates (Male, unadjusted (Figure 1B); Male, adjusted: 16.93 (16.25, 17.61) and 35.69 (33.09, 38.29); Female, unadjusted (Figure 1C); Female, adjusted: 16.71 (15.94, 17.47) and 36.06 (34.62, 37.49)). However, the slopes of the various segments by sex were significantly different in all three age windows: 8 to <17 years, 17 to <37 years, and 37 to 55 years (Table 3). Prior to age 17, female CVH holds steady while male CVH decreased 0.01 points per year (95% confidence interval: -0.02, -0.01; P=0.001 for difference between sexes). Between 17 and 37, CVH declined at a faster rate for men compared to women (-0.09 vs -0.06; P<0.001). After age 37, CVH declined more rapidly for women compared to men (-0.09 vs -0.07; P<0.001), which suggests a different pattern of change by sex. Models stratified by sex and race were not substantively different from the models stratified by sex only (Web Table 3 and Web Figure 2).

The sex-specific means at each influential age (8, 17, 37 and 55 years) help to further explain the differences in the change in CVH score over time (Table 4 and Web Figure 3). Behavioral metrics, diet, physical activity and smoking were collected less frequently than the clinical metrics, mean scores (poor (0) to ideal (2)) are shown in Web Table 4.

BMI increases steadily for both males and females over time, however the difference between the two sexes is not significant at any of the four ages. The change in BMI over time is consistent
with the change in overall score over time in that it remains at ideal levels at age 8 and 17, declines to intermediate by age 37 and to poor by age 55. Blood pressure starts out similarly for males (97/44 mmHg) and females (97/45 mmHg). While mean systolic and diastolic BP both increase for each sex, they remain at ideal levels through age 55. Males have a steeper increase in systolic BP than females prior to age 17 (+6.0 mmHg), but after holding relatively steady between 17 and 37, increase less between 37 and 55 years compared to females (5.2 vs 7.9 mmHg). Males and Females have a similar increase in diastolic blood pressure prior to age 17. Between 17 and 37 males increase and then decrease slightly after 37, where females increase less steeply between 17 and 37 and continue to increase after 37. Mean total cholesterol and fasting blood glucose are significantly different by sex at all four ages. Female total cholesterol declines from age 8 to 17 (168 mg/dL to 163 mg/dL) and then increases at age 37 and increases again to reach intermediate levels at age 55. Male total cholesterol declines from age 8 to 17 (164 to 151 mg/dL), increases to 193 mg/dL at age 37, and decreases to 182 mg/dL at age 55. Male total cholesterol is lower than female at all ages except 37 years. Males blood glucose levels increase more than females in every age period. Female blood glucose levels consistently increase over time from 80.7 mg/dL at age 8 to 95.9 mg/dL at age 55.

In a sensitivity analysis including 14,422 individuals with complete parental education data, results were similar between the models with and without adjusting for parental education (16.2 years, 95% CI: 15.5, 16.8) and 39.8 years (35.8, 43.8) without adjusting for parental education compared to 16.1 years (95% CI: 15.4, 16.7) and 39.3 years (35.5, 43.0) with adjustment).

DISCUSSION

Within this pooled cohort there were influential periods in adolescence and adulthood when the loss of clinical CVH is accelerated. The largest acceleration in the age-related loss of clinical
CVH occurred at the first change point, approximately age 17 years. A second, less dramatic acceleration in the age-related decline in clinical CVH occurred at the second change point in middle age, 37 years. These ages (approximately 17 and 37 years) appear to coincide with social and developmental transitions providing unique insight to the development of preventive interventions tailored to these specific phases in life (18). CVH score slopes between change points as well as the patterns of change for the individual metrics comprising the score differed by sex, suggesting the potential importance of sex-specific interventions.

At age seventeen, adolescents typically gain increased independence from their parents, and transition between pediatric and adult healthcare practitioners. Many adolescents leave their provider’s practice between ages 15-22, mainly due to aging out or completely dropping out of primary care (19,20). This poses challenges for intervention, due to interrupted continuity of care. Males tend to have a longer gap in care than females (21). Changes in schedules, school, and jobs may interfere with meeting guidelines for healthy sleep, physical activity, and diet (22). There is also a large shift in personal responsibility, greater financial independence with access to tobacco, greater personal choices around food selection, alcohol use, and physical activity at this time. These behaviors are important for achieving and maintaining ideal CVH (2). We observed low mean scores for diet among 17 year olds, suggesting that diet may be an important lifestyle behavior to potentially target for intervention.

At approximately age 37, adults transition from young adulthood to middle age. The increasing personal, professional and social pressures encountered during this phase of life may further compete with adherence to healthy lifestyle leading to diminished levels of clinical risk factors. Employment-based wellness programs could help facilitate maintenance of CVH during this period.
Although the second change point at age 37 is slight in the overall model, there is a significant difference by sex thereby illustrating changes men and women experience over time. Our results show that while women maintain a higher CVH score through age 37, their rate of decline is significantly greater than that of men between ages 37 and 55. These results support well-documented data showing that males and females differ in their trajectories regarding CVH risk factor development over time (22). While much remains unknown about CVH during and after pregnancy in women, recent literature documents that pregnant women between the ages of 20 to 44 are significantly less likely to maintain ideal CVH compared with non-pregnant women in the same age range (23). The second change point falls squarely during women’s reproductive years and could be a contributing factor in the difference between men and women during this time. In addition to the difference in CVH decline, there are also differences in healthcare utilization by sex (24,25). Men are less likely than women to utilize health care services or make preventive care visits despite declining health comparable to that of women (25).

Our findings on the age-related changes of individual CVH metrics complement prior work. Specifically, most prior cross-sectional and cohort studies report that BMI increases with age, possibly leveling out in older age (26-32). Although trends in BMI over time in this study did not significantly differ by sex, prior literature suggests and we concur that ideally intervention should differ for men and women (26). For example, Li et. al concluded that high or increasing BMI at any life stage is associated with a high adult BP (33). While blood pressure increased over time in our data, on average it remained higher in males than females at most points after age 8 (33). These seven metrics are synergistic in children and young adults with co-morbidities (34). Risk behaviors are interrelated—intervention in one can affect another (22).
We know that risk of cardiovascular disease is established long before middle age (35) and with primary and primordial prevention, cardiovascular disease can be prevented (36). The World Health Organization strongly recommends primordial and primary prevention of major known risk factors for noncommunicable diseases such as cardiovascular disease to begin early in life (37). Longitudinal analyses of CVH have shown that maintaining CVH from childhood onward reduces the risk for cardiovascular disease in adulthood (4,5).

Our approach to determining influential age windows when loss of cardiovascular health accelerates has several strengths, including the large dataset with multiple observations for individuals from childhood through middle age. The method for determining change points accounts for repeated measures within individuals as well as using a likelihood based approach that doesn’t require any prior assumptions (14). Two of the five cohorts in this pooled cohort analysis are entirely White, therefore a limitation of our work is that we were unable to estimate differences in change points or slopes by race without essentially performing cohort-specific analyses. While we attempted to deal with cohort-specific differences by adjusting all models by cohort, there have been changes over time in standards of care and of public health messaging that may differ between the US and Finland, and within these countries over time. Future studies will be needed to examine how changes in clinical, behavioral and cultural factors may impact these influential periods. Research has shown patterns of change in CVH may differ within a population. However, in multiple studies on CVH trajectories there is a decline in CVH during childhood and early adolescence and there appears to be a change point near age 17 for all trajectory groups (4,5) which supports the population-level influential age windows estimated here. In looking into the means in each metric by age and sex, we were not able to take medication usage into account as is done in the CVH score. So trends in BP, cholesterol and
blood glucose may appear to be attenuated due to medications used to control these factors. Additionally, data on CVH behaviors are sparse, particularly in younger ages, so we were not able to estimate change points in the full CVH score including these observations. Our data begin at age 8, therefore we cannot generalize how and when changes in overall CVH may occur in children younger than 8 years old from these data, but this should a topic of future investigation. While we did estimate change points separately by sex, we did not have menopausal status available to us from every cohort, therefore, these biological changes were not included in our analysis.

In conclusion, adolescence and young adulthood are key age windows when age-related loss of clinical CVH greatly accelerates. Trends in CVH are not consistent by sex, and identification of specific age-windows offers an opportunity for personalized preventive intervention. Additional research identifying the specific factors leading to accelerated loss of CVH in adolescence and middle adulthood is needed. The creation of personalized interventions targeted to these critical age windows may offer new tools to preserve ideal CVH throughout the lifetime.

ACKNOWLEDGEMENTS

The authors thank Arja Kylliäinen for excellence in data management with the Young Finns Study and the Special Turku Coronary Risk Factor Intervention Praoject.

Conflict of Interest: None declared.

Data Availability: Data are available upon approval from each of the cohorts in this study (Bogalusa Heart Study, CARDIA, Project HeartBeat!, STRIP, and Young Finns).
References

1. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. *NCHS Data Brief.* 2018(328):1-8.
2. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation.* 2010;121(4):586-613.
3. Lloyd-Jones DM. Cardiovascular health and protection against CVD: more than the sum of the parts? *Circulation.* 2014;130(19):1671-1673.
4. Allen NB, Kefman AE, Labarthe D, et al. Cardiovascular Health Trajectories From Childhood Through Middle Age and Their Association with Subclinical Atherosclerosis. *JAMA Cardiol.* 2020;5(5):1-10.
5. Pollock BD, Stuchlik P, Harville EW, et al. Life course trajectories of cardiovascular risk: Impact on atherosclerotic and metabolic indicators. *Atherosclerosis.* 2019;280:21-27.
6. Labarthe DR, Dai S, Day RS, et al. Project HeartBeat! Concept, development, and design. *Am J Prev Med.* 2009;37(1 Supp):S9-16.
7. Raitakari OT, Juonala M, Ronnemaa T, et al. Cohort profile: the cardiovascular risk in Young Finns Study. *Int J Epidemiol.* 2008;37(6):1220-1226.
8. Berenson GS. Bogalusa Heart Study: a long-term community study of a rural biracial (black/white) population. *The American journal of the medical sciences.* 2001;322(5):267-274.
9. Friedman GD, Cutter GR, Donahue RP, et al. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology.* 1988;41(11):1105-1116.
10. Simell O, Niinikoski H, Rönnemaa T, et al. Cohort Profile: The STRIP Study (Special Turku Coronary Risk Factor Intervention Project), an Infancy-onset Dietary and Lifestyle Intervention Trial. *International Journal of Epidemiology.* 2009;38(3):650-655.
11. Division of Nutrition PA, and Obesity. A SAS Program for the 2000 CDC Growth Charts (ages 0 to <20 years). Centers for Disease Control and Prevention. [http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm](http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm). Published 2016. Accessed 12/10/2015, 2015.
12. Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents. *Pediatrics.* 2017;140(3).
13. Steinberger J, Daniels SR, Hagberg N, et al. Cardiovascular Health Promotion in Children: Challenges and Opportunities for 2020 and Beyond: A Scientific Statement From the American Heart Association. *Circulation.* 2016;134(12):e236-255.
14. Muggeo V. Segmented mixed models with random changepoints in R [Working Paper]. 2016. doi:10.13140/RG.2.1.4180.8402. Published February 2016. Accessed September 9, 2020.
15. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC. *nlme: Linear and nonlinear mixed effects models. R package version.* 2013;3(1):111.
16. Team RC. *R: A language and environment for statistical computing.* Vienna, Austria: R Foundation for Statistical Computing; 2017.
17. Muggeo VM, Atkins DC, Gallop RJ, Dimidjian S. Segmented mixed models with random changepoints: a maximum likelihood approach with application to treatment for depression study. *Statistical Modelling.* 2014;14(4):293-313.

18. Sable C, Foster E, Uzark K, et al. Best practices in managing transition to adulthood for adolescents with congenital heart disease: the transition process and medical and psychosocial issues: a scientific statement from the American Heart Association. *Circulation.* 2011;123(13):1454-1485.

19. Burke R, Spoerri M, Price A, Cardosi A-M, Flanagan P. Survey of primary care pediatricians on the transition and transfer of adolescents to adult health care. *Clinical Pediatrics.* 2008;47(4):347-354.

20. White PH, Cooley WC. Supporting the Health Care Transition From Adolescence to Adulthood in the Medical Home. *Pediatrics.* 2018;142(5):e20182587.

21. Wisk LE, Finkelstein JA, Sawicki GS, et al. Predictors of timing of transfer from pediatric- to adult-focused primary care. *JAMA Pediatr.* 2015;169(6):e150951.

22. Institute NHLAb. Challenges and opportunities for the prevention and treatment of cardiovascular disease among young adults. [https://www.nhlbi.nih.gov/events/2017/challenges-and-opportunities-prevention-and-treatment-cardiovascular-disease-among](https://www.nhlbi.nih.gov/events/2017/challenges-and-opportunities-prevention-and-treatment-cardiovascular-disease-among). Published 2017. Accessed August 11, 2020.

23. Perak AM, Ning H, Khan SS, Van Horn LV, Grobman WA, Lloyd-Jones DM. Cardiovascular Health Among Pregnant Women, Aged 20 to 44 Years, in the United States. *Journal of the American Heart Association.* 2020;9(4):e015123.

24. White A, Lockyer L. Tackling coronary heart disease. *Bmj.* 2001;323(7320):1016-1017.

25. Pinkhasov RM, Wong J, Kashanian J, et al. Are men shortchanged on health? Perspective on health care utilization and health risk behavior in men and women in the United States. *Int J Clin Pract.* 2010;64(4):475-487.

26. Ostbye T, Malhotra R, Landerman LR. Body mass trajectories through adulthood: results from the National Longitudinal Survey of Youth 1979 Cohort (1981-2006). *Int J Epidemiol.* 2011;40(1):240-250.

27. Clarke P, O'Malley PM, Johnston LD, Schulenberg JE. Social disparities in BMI trajectories across adulthood by gender, race/ethnicity and lifetime socio-economic position: 1986-2004. *Int J Epidemiol.* 2009;38(2):499-509.

28. Sheehan TJ, DuBrava S, DeChello LM, Fang Z. Rates of weight change for black and white Americans over a twenty year period. *Int J Obes Relat Metab Disord.* 2003;27(4):498-504.

29. Thorpe RJ, Jr., Ferraro KF. Aging, Obesity, and Mortality: Misplaced Concern About Obese Older People? *Res Aging.* 2004;26(1):108-129.

30. Barone BB, Clark JM, Wang NY, Meoni LA, Klag MJ, Brancati FL. Lifetime weight patterns in male physicians: the effects of cohort and selective survival. *Obesity (Silver Spring).* 2006;14(5):902-908.

31. Lewis CE, Smith DE, Wallace DD, Williams OD, Bild DE, Jacobs DR, Jr. Seven-year trends in body weight and associations with lifestyle and behavioral characteristics in black and white young adults: the CARDIA study. *Am J Public Health.* 1997;87(4):635-642.

32. Ferraro KF, Thorpe RJ, Jr., Wilkinson JA. The life course of severe obesity: does childhood overweight matter? *J Gerontol B Psychol Sci Soc Sci.* 2003;58(2):S110-S119.
33. Li L, Law C, Power C. Body mass index throughout the life-course and blood pressure in mid-adult life: a birth cohort study. *Journal of Hypertension*. 2007;25(6):1215-1223.
34. Berenson GS, Srinivasan SR, Bao W, Newman WP, 3rd, Tracy RE, Wattigney WA. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. The Bogalusa Heart Study. *The New England journal of medicine*. 1998;338(23):1650-1656.
35. McCarron P, Smith GD, Okasha M, McEwen J. Blood pressure in young adulthood and mortality from cardiovascular disease. *Lancet*. 2000;355(9213):1430-1431.
36. Weintraub WS, Daniels SR, Burke LE, et al. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. *Circulation*. 2011;124(8):967-990.
37. Aboderin I, Kalache, A., Ben-Shlomo, Y., Lynch, J.W., Yajnik, C.S., Kuh, D., Yach, D. Life Course Perspectives on Coronary Heart Disease, Stroke and Diabetes: Key Issues and Implications for Policy and Research. In. Geneva: World Health Organization; 2002.
Table 1. Clinical Cardiovascular Health Score Components

| Health category | Body Mass Index\(^a\) | Total Cholesterol, mg/dL | Blood Pressure, mmHg | Fasting Blood Glucose, mg/dL |
|-----------------|------------------------|--------------------------|----------------------|----------------------------|
|                 | Age ≥20 years | Age <20 years | Age ≥20 years | Age <20 years | Age ≥18 years | Age <18 years | Age ≥20 years | Age <20 years |
| Ideal health    | <25.0        | <85\textsuperscript{th} percentile | <185, unmedicated | <185, unmedicated | <120/80, unmedicated | <90\textsuperscript{th} percentile | <100, unmedicated | <100, unmedicated |
| Intermediate health | 25.0-29.99 | 85\textsuperscript{th}-95\textsuperscript{th} percentile | 185-219 or treated to <185 | 185-219 or treated to <185 | SBP 120-139 or DBP 80-89, or treated to <120/80 | 90\textsuperscript{th}-95\textsuperscript{th} percentile or SBP≥120 or DBP≥80 | 100-125 or treated to <100 | 100-125 or treated to <100 |
| Poor health     | ≥30.0        | >95\textsuperscript{th} percentile | ≥220          | ≥220          | SBP≥140 or DBP≥90 | >95\textsuperscript{th} percentile | ≥126         | ≥126         |

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure. \(^a\)Weight (kg)/height (m)\(^2\)
Table 2. Demographics, clinical measures, and covariates at each individual’s first exam, by sex. CVH pooled cohort\(^a\) (1973 to 2012).

| Characteristics                 | Male (N=8882) | Female (N=9461) |
|---------------------------------|---------------|-----------------|
|                                 | Mean (SD)     | No. %           | Mean (SD)     | No. %           |
| **White**                       |               |                 |               |                 |
| Age, years                      | 17.4 (8.1)    | 6058 68.2       | 17.8 (8.1)    | 6288 66.4       |
| **Cohort**                      |               |                 |               |                 |
| Young Finns                     | 1486          | 16.7            | 1650          | 17.4            |
| Project HeartBeat!              | 201           | 2.3             | 208           | 2.2             |
| CARDIA                          | 2315          | 26.1            | 2783          | 29.4            |
| Bogalusa Heart Study            | 4628          | 52.1            | 4582          | 48.4            |
| STRIP                           | 252           | 2.8             | 238           | 2.5             |
| **Clinical measures**           |               |                 |               |                 |
| BMI\(^b\)                       | 21.3 (4.9)    |                 | 21.5 (5.5)    |                 |
| BMI %, by age and sex\(^c\)     | 52.8 (29.9)   |                 | 53.5 (30.1)   |                 |
| SBP, mmHg                       | 109.5 (13.1)  |                 | 105.9 (11.1)  |                 |
| SBP %\(^d\)                    | 47.7 (27.0)   |                 | 50.2 (26.8)   |                 |
| DBP, mmHg                       | 59.1 (15.1)   |                 | 59.4 (13.0)   |                 |
| DBP %\(^d\)                    | 24.9 (22.4)   |                 | 28.9 (24.1)   |                 |
| Total cholesterol, mg/dL        | 169.8 (34.0)  |                 | 173.2 (33.1)  |                 |
| Fasting glucose, mg/dL          | 85.9 (12.7)   |                 | 83.0 (14.4)   |                 |
| **Ideal behavior scores\(^e\)**|               |                 |               |                 |
| Smoking                         | 4922          | 62.4            | 5541          | 64.8            |
| Diet                            | 1088          | 23.6            | 1793          | 32.6            |
| Physical activity               | 1781          | 38.3            | 1179          | 22.4            |
| **Maternal education\(^f\)**   |               |                 |               |                 |
| ≤ 6 years                       | 231           | 3.6             | 313           | 4.3             |
| 7-9 years                       | 971           | 14.9            | 1131          | 15.5            |
| 10-12 years                     | 2869          | 44.1            | 3164          | 43.4            |
| 13-16 years                     | 1947          | 29.9            | 2176          | 29.8            |
| >16 years (grad school)         | 483           | 7.4             | 508           | 7.0             |
| **Paternal education\(^f\)**   |               |                 |               |                 |
| ≤ 6 years                       | 270           | 4.7             | 361           | 5.7             |
| 7-9 years                       | 1045          | 18.3            | 1215          | 19.0            |
| 10-12 years                     | 2348          | 41.1            | 2574          | 40.3            |
| 13-16 years                     | 1609          | 28.1            | 1719          | 26.9            |
| >16 years (grad school)         | 447           | 7.8             | 514           | 8.1             |
| **Clinical CVH Score**          | 6.8 (1.3)     |                 | 7.0 (1.2)     |                 |

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; STRIP, Special Turku Coronary Risk Factor Intervention Project; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CVH, cardiovascular health; SD, standard deviation

\(^a\)CVH pooled cohort consists of Bogalusa Heart Study, CARDIA, Project HeartBeat!, STRIP, and Young Finns.

\(^b\)Weight (kg)/height (m)^2\(^c\)BMI% only available for those who were <20 years old at baseline. In analytical sample: BMI% N=11,777; \(^d\)SBP%, and DBP% only available for those who were <18 years old at baseline. In analytic sample: BP% N=10,627. \(^e\)Behavior scores were not captured at the first visit for every participant—these scores represent their first available score for that behavior. \(^f\)Parent education data were not available for all individuals.
Table 3. Mixed Model Parameter Estimates of Mean Clinical Cardiovascular Health Score\(^a\) Over Time, by Sex. CVH pooled cohort\(^b\) (1973 to 2012).

| CVH Outcomes                          | Unadjusted | Total Δ or difference over segment | Adjusted\(^c\) | Total Δ or difference over segment |
|---------------------------------------|------------|-----------------------------------|----------------|-----------------------------------|
|                                       | Mean       | 95% CI   | P             | Mean       | 95% CI   | P             |
| Mean CVH score for 8-year-olds        |            |          |               |            |          |               |
| Female (reference)                    | 7.09       | 7.05 to 7.13 | <.001 | 6.95       | 6.89 to 7.00 | <.001 |
| Male                                  | 7.15       | 7.11 to 7.19 | <.001 | 7.00       | 6.94 to 7.06 | <.001 |
| Difference in mean CVH score for 8-year-olds between sexes | 0.06       | 0.00 to 0.11 | 0.04 | 0.05       | 0.00 to 0.11 | 0.06 |
| Segment-specific slope (Δ/year)       |            |          |               |            |          |               |
| Female Age 8 to 16.9 years            | 0.00       | -0.01 to 0.01 | 0.83 | 0.01       | 0.00 to 0.01 | 0.38 |
|                                       | -0.06      | -0.06 to -0.06 | <.001 | -1.21      | -0.06 to -0.06 <.001 | -1.2 |
|                                       | -0.09      | -0.09 to -0.09 | <.001 | -1.63      | -0.09 to -0.09 <.001 | -1.63 |
| Male Age 8 to 16.9 years              | -0.01      | -0.02 to -0.01 | <.001 | -0.12      | -0.02 to 0.00 <.001 | -0.12 |
|                                       | -0.09      | -0.09 to -0.09 | <.001 | -1.8       | -0.09 to -0.09 <.001 | -1.79 |
|                                       | -0.07      | -0.07 to -0.06 | <.001 | -1.24      | -0.07 to -0.06 <.001 | -1.25 |
| Difference in segment-specific slope between sexes |          |          |               |            |          |               |
| Age 8 to 16.9 years: Male - Female    | -0.01      | -0.02 to -0.01 | 0.001 | -0.13      | -0.02 to -0.01 <.001 | -0.13 |
| Age 17 to 36.9 years: Male - Female   | -0.03      | -0.03 to -0.03 | <.001 | -0.59      | -0.03 to -0.03 <.001 | -0.59 |
| Age 37 to 55 years: Male - Female     | 0.02       | 0.02 to 0.03 | <.001 | 0.38       | 0.02 to 0.03 <.001 | 0.38 |

Abbreviations: CVH, cardiovascular health. \(^a\)Clinical CVH score ranges from 0 to 8 with 8 being the most ideal. \(^b\)CVH pooled cohort consists of Bogalusa Heart Study, CARDIA, Project HeartBeat!, STRIP, and Young Finns. \(^c\)Adjusted for age at baseline, race, and cohort. Numbers presented are for Black individuals from Bogalusa.
Table 4. Mean Values of Each Clinical Metric at the Change Points, by Sex. CVH pooled cohort\(^a\) (1973 to 2012).

| Clinical Metric                  | 8-year-olds                  | 17-year-olds                  | 37-year-olds                  | 55-year-olds                  |
|----------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
|                                  | Female                       | Male                         | Female                       | Male                         | Female                       | Male                         | Female                       | Male                         |
|                                  | Mean  SD                      | Mean  SD                      | Difference  95% CI           | Mean  SD                      | Mean  SD                      | Difference  95% CI           | Mean  SD                      | Mean  SD                      | Difference  95% CI           |
| BMI\(^b\)                        | 17.2  3.1                     | 17.0  2.9                     | -0.2 -0.5 to 0.1             | 22.2  4.5                     | 22.3  4.1                     | 0.1 -0.3 to 0.5              | 31.4  7.7                     | 30.3  6.1                     | -1.1 -2.6 to 0.4             |
| Systolic BP, mmHg                | 96.5  8.8                     | 96.8  8.3                     | 0.3 -0.6 to 1.2              | 110.7 9.0                     | 117 11.7                      | 6.3 5.2 to 7.4\(^c\)         | 117.6 15.9                    | 121.4 15.9                    | 3.7 0.2 to 7.3\(^c\)         |
| Diastolic BP, mmHg               | 45.1 12.0                     | 44.1 10.9                     | -1.0 -2.1 to 0.2             | 61.1 8.6                      | 59.6 10.3                     | -1.5 -2.4 to -0.5\(^c\)      | 61.4 8.2                      | 58.6 10.3                     | -2.8 -3.5 to -1.8\(^c\)      |
| Total Cholesterol, mg/dL         | 167.6 27.9                    | 164.2 25.8                    | -3.4 -6.1 to -0.6\(^c\)      | 163.3 30.6                    | 151.1 28.2                    | -12.2 -15.2 to -9.2\(^c\)    | 201.7 36.3                    | 182.4 35.9                    | -19.3 -27.4 to -11.2\(^c\)   |
| Fasting Blood Glucose, mg/dL     | 80.7 8.0                      | 82.4 9.0                      | 1.8 0.9 to 2.6\(^c\)         | 81.6 8.2                      | 86 8.4                        | 4.4 3.5 to 5.2\(^c\)         | 95.9 15.8                     | 104 21.9                      | 8 3.6 to 12.4\(^c\)          |

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; SD, standard deviation. \(^a\)CVH pooled cohort consists of Bogalusa Heart Study, CARDIA, Project HeartBeat!, STRIP, and Young Finns. \(^b\)Weight (kg)/height (m)\(^2\) \(^c\)p<0.05 for t-test.
Figure Legends

Figure 1. Plots of Unadjusted Segmented Mixed Models (fixed effects only), CVH pooled cohort (1973 to 2012). A) Overall Model (change points: 17.3 and 35.1, 95%CI: 16.8, 17.8 and 32.3, 37.9). Stratified Models: B) Males (change points: 17.1 and 37.2, 95%CI: 16.9, 18.3 and 33.7, 40.6), and C) Females (change points: 16.8 and 35.6, 95%CI: 16.1, 17.6 and 34.3, 36.9). (For illustrative purposes data points from 50 randomly selected participants are shown).

Abbreviations: CVH, cardiovascular health.

Figure 2. Adjusted Segmented Mixed Model, by Sex. (The reference group, Black males and females from Bogalusa Heart Study (1973 to 2010), is shown here. Dashed vertical lines indicate the knots at 17 and 37 years. Clinical CVH score ranges from 0 to 8 with 8 being the most ideal.)

Abbreviations: CVH, cardiovascular health.
