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Primordial Prevention of Cardiovascular Disease

Matthew W. Gillman, MD, SM

Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Department of Nutrition, Harvard School of Public Health, Boston, MA

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While primary prevention is about treating risk factors to prevent cardiovascular disease, primordial prevention refers to avoiding the development of risk factors in the first place.¹ Because atherosclerosis starts in youth and is related to dyslipidemia, to smoking, and to higher blood pressure, glucose levels and body mass index, the implication is that primordial prevention must start early in life.¹ Additional support for early prevention arises from recent data on ideal cardiovascular health. Using similar definitions of ideal cardiovascular health, comprising 3 health factors and 4 health behaviors, both the Cardiovascular Risk in Young Finns Study and the Special Turku Coronary Risk Factor Intervention Project for Children (STRIP) showed that the number of ideal metrics is lower in late v. early adolescence.^{2, 3} In cross-sectional NHANES data, this apparent pattern of declining prevalence of ideal cardiovascular health with age continues from adolescence through adulthood.^{4, 5}

When and how to intervene to maintain ideal cardiovascular health factors, with which almost all babies are born, are vexing but critical questions. Over the past two decades, a literature has emerged suggesting that starting interventions very early—as early as infancy and perhaps before—may be an especially effective approach to prevent chronic disease over the life course.^{6, 7} The “first 1000 days” from conception to preschool ages are a period of maximal developmental plasticity. Prevention interventions during this period may thus set individuals on the best possible trajectories of lifelong cardiovascular health, whereas later interventions, even those in later childhood or adolescence, may be stymied by inadequate physiological responses. This paradigm rests on the notion of critical or sensitive periods, during which modification of relevant exposures has lasting impact. Outside of this period, there is little or no impact.⁸

Address for Correspondence: Matthew W. Gillman, MD, SM, Harvard Medical School and Harvard Pilgrim Health Care Institute, 133 Brookline Ave., 6th floor, Boston, MA 02215, Phone: 617-509-9968, Fax: 617-859-9853, Matthew_gillman@hms.harvard.edu.

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Many animal experiments suggest that the critical period mechanism is at play in the origins of adult cardio-metabolic outcomes.⁹ However, some pathophysiologic process, perhaps including atherosclerosis, can arise from accumulation of damage over time from an increasing number or duration of risk factors, rather than from particular insults during a critical or sensitive period of early development. Such a process would imply that sustained interventions to reduce the onset or progression of pathology may be required. In the primordial prevention of cardiovascular disease, questions remain about the extent to which early interventions alone are adequate, whether they need to be continued or augmented later, or whether waiting to intervene is the best strategy.

STRIP comprises a prevention intervention begun in infancy that was continued and augmented throughout childhood into adolescence. In the early 1990s, its investigators randomly allocated over 1000 infants to an individualized dietary intervention v. usual care, and they visited the participants for intervention or assessment at least biannually until the age of 20 years. The principal dietary goal was replacement of saturated fat with unsaturated fat, accompanied by promotion of intake of fruits, vegetables, and whole grains, reduction of salt intake, and reasonable portion sizes. Smoking prevention counseling started at age 8 years.

In this issue of *Circulation*, STRIP investigators report the effect of the intervention on the prevalence of the metabolic syndrome among 15-20-year-old participants.¹⁰ Overall they observed a reduction in prevalence among control v. intervention participants from 10-13% to 6-7%. The results were robust to the definition of metabolic syndrome, and they were driven by reductions in high blood pressure in both sexes and high triglycerides among boys. There was less evidence for reductions in high glucose and high waist circumference, and no effect on low HDL-cholesterol. Although statistical power was adequate, the internal validity of the findings may have been compromised by an approximately 50% loss to followup since infancy, which was higher in the intervention than control group, although the authors point out that attrition was not related to behavioral or physiological measures. Blinding is not mentioned; nonetheless one would expect little bias because outcomes were laboratory measures except for waist circumference.

The results of this STRIP analysis complement their other published findings.¹¹ Two years ago they reported a beneficial effect of the intervention on ideal cardiovascular health, which was driven by better diet and decreased total cholesterol and blood pressure.³ While metabolic syndrome contains only some factors that overlap with ideal cardiovascular health, these two complementary combinations of factors anchor the harm and benefit ends of the cardiovascular risk spectrum. In other analyses with single outcomes, the intervention showed modest intervention effects on lowering adolescent blood pressure and insulin resistance, an increase in arterial flow-mediated dilation in boys mediated by changes in lipid levels, and a decrease in overweight among girls.¹¹⁻¹⁴ STRIP investigators have reassuringly reported that the intervention had no adverse effects on height, cognition, pubertal timing, or age at menarche, although there was also no effect on fitness level or arterial distensibility.¹⁵ While the investigators measured carotid intima-media thickness and left ventricular hypertrophy, it is not apparent that they have reported intervention effects on these outcomes.

Given that one of the most robust findings from STRIP is blood pressure reduction, it is instructive to compare it with two other randomized trials with adolescent followup whose intervention periods were limited to infancy. In a study of sodium restriction for the first 6 months of life, systolic blood pressure was 2.1 mm Hg lower (90% confidence interval -3.7 to -0.5) among intervention than control participants at 25 weeks of age, the end of the intervention period.¹⁶ At age 15 years, the investigators were able to follow up 167 of the original 466 participants, at which time the long-term covariate-adjusted intervention effect on systolic blood pressure was -3.6 mm Hg (95 % confidence interval -6.6 to -0.5).¹⁷ The other study, the Promotion of Breastfeeding Intervention Trial (PROBIT), is a cluster randomized trial of promoting breastfeeding duration and exclusivity among nursing mothers. At 11.5 years of age, the effect on systolic blood pressure was +1.0 mm Hg (-1.1 to 3.1).¹⁸ These values compare to an average intervention effect of -1.0 mm Hg (95% confidence interval -1.7 to -0.2) from age 7 months to 15 years in STRIP (Table 1).¹⁹

These three trials, one starting in infancy and continuing through adolescence, and two limited to infancy alone, provide evidence that repeated advice on healthful diet or sodium restriction during infancy may lower later blood pressure. Breastfeeding promotion, however, did not. They underpin recommendations to limit salt intake, substitute unsaturated for saturated fats, and promote more healthful foods starting in infancy and toddlerhood.²⁰ It is too much to ask of these studies alone, however, to solve the generic dilemmas about when to start, and how long to continue, early life prevention interventions, as well as to specify the most effective and sustainable approaches. We must continue to build the evidence base for primordial prevention on the totality of the evidence, which involves judiciously uniting findings from long-term observational cohorts that incorporate repeated measures, experiments among animals with shorter life spans than humans, and human intervention studies that rely on surrogate endpoints, such as blood pressure, that are causally related to later cardiovascular outcomes.

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References

1. McGill HC Jr, McMahan CA. Determinants of atherosclerosis in the young. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Research Group. *Am J Cardiol.* 1998; 82:30T–36T.
2. Laitinen TT, Pahkala K, Magnussen CG, Viikari JS, Oikonen M, Taittonen L, Mikkilä V, Jokinen E, Hutri-Kahonen N, Laitinen T, Kahonen M, Lehtimäki T, Raitakari OT, Juonala M. Ideal cardiovascular health in childhood and cardiometabolic outcomes in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation.* 2012; 125:1971–1978. [PubMed: 22452832]
3. Pahkala K, Hietalampi H, Laitinen TT, Viikari JS, Ronnema T, Niinikoski H, Lagstrom H, Talvia S, Jula A, Heinonen OJ, Juonala M, Simell O, Raitakari OT. Ideal cardiovascular health in adolescence: effect of lifestyle intervention and association with vascular intima-media thickness and elasticity (the Special Turku Coronary Risk Factor Intervention Project for Children [STRIP] study). *Circulation.* 2013; 127:2088–2096. [PubMed: 23613255]
4. Shay CM, Ning H, Allen NB, Carnethon MR, Chiuve SE, Greenlund KJ, Daviglius ML, Lloyd-Jones DM. Status of cardiovascular health in US adults: prevalence estimates from the National Health

- and Nutrition Examination Surveys (NHANES) 2003-2008. *Circulation*. 2012; 125:45–56. [PubMed: 22095826]
5. Shay CM, Ning H, Daniels SR, Rooks CR, Gidding SS, Lloyd-Jones DM. Status of cardiovascular health in US adolescents: prevalence estimates from the National Health and Nutrition Examination Surveys (NHANES) 2005-2010. *Circulation*. 2013; 127:1369–1376. [PubMed: 23547177]
 6. Gillman MW, Ludwig DS. How early should obesity prevention start? *N Engl J Med*. 2013; 369:2173–2175. [PubMed: 24224559]
 7. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev*. 2014; 94:1027–1076. [PubMed: 25287859]
 8. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. *Int J Epidemiol*. 2002; 31:285–293. [PubMed: 11980781]
 9. McMillen IC, Robinson JS. Developmental origins of the metabolic syndrome: prediction, plasticity, and programming. *Physiol Rev*. 2005; 85:571–633. [PubMed: 15788706]
 10. Nupponen M, Pahkala K, Juonala M, Magnussen C, Niinkoski H, Rönnemaa T, Viikari J, Saarinen M, Lagström H, Jula A, Simell O, Raitakari O. Metabolic Syndrome from Adolescence to Early Adulthood -Effect of Infancy-onset Dietary Counseling of Low-Saturated-Fat. The Special Turku Coronary Risk Factor Intervention Project (STRIP). *Circulation*. 2015; 131:XX–XXX.
 11. Magnussen CG, Niinkoski H, Juonala M, Kivimäki M, Ronnemaa T, Viikari JS, Simell O, Raitakari OT. When and how to start prevention of atherosclerosis? Lessons from the Cardiovascular Risk in the Young Finns Study and the Special Turku Coronary Risk Factor Intervention Project. *Pediatr Nephrol*. 2012; 27:1441–1452. [PubMed: 21877168]
 12. Hakanen M, Lagstrom H, Kaitosaari T, Niinkoski H, Nanto-Salonen K, Jokinen E, Sillanmäki L, Viikari J, Ronnemaa T, Simell O. Development of overweight in an atherosclerosis prevention trial starting in early childhood. The STRIP study. *Int J Obes (Lond)*. 2006; 30:618–626. [PubMed: 16446743]
 13. Niinkoski H, Lagstrom H, Jokinen E, Siltala M, Ronnemaa T, Viikari J, Raitakari OT, Jula A, Marniemi J, Nanto-Salonen K, Simell O. Impact of repeated dietary counseling between infancy and 14 years of age on dietary intakes and serum lipids and lipoproteins: the STRIP study. *Circulation*. 2007; 116:1032–1040. [PubMed: 17698729]
 14. Oranta O, Pahkala K, Ruottinen S, Niinkoski H, Lagstrom H, Viikari JS, Jula A, Loo BM, Simell O, Ronnemaa T, Raitakari OT. Infancy-onset dietary counseling of low-saturated-fat diet improves insulin sensitivity in healthy adolescents 15-20 years of age: the Special Turku Coronary Risk Factor Intervention Project (STRIP) study. *Diabetes Care*. 2013; 36:2952–2959. [PubMed: 23801725]
 15. Mikola H, Pahkala K, Ronnemaa T, Viikari JS, Niinkoski H, Jokinen E, Salo P, Simell O, Juonala M, Raitakari OT. Distensibility of the aorta and carotid artery and left ventricular mass from childhood to early adulthood. *Hypertension*. 2015; 65:146–152. [PubMed: 25350980]
 16. Hofman A, Hazebroek A, Valkenburg HA. A randomized trial of sodium intake and blood pressure in newborn infants. *JAMA*. 1983; 250:370–373. [PubMed: 6343656]
 17. Geleijnse JM, Hofman A, Witteman JC, Hazebroek AA, Valkenburg HA, Grobbee DE. Long-term effects of neonatal sodium restriction on blood pressure. *Hypertension*. 1997; 29:913–7. [PubMed: 9095076]
 18. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, Gusina N, Foo Y, Palmer T, Thompson J, Gillman MW, Smith GD, Oken E. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. *Circulation*. 2014; 129:321–329. [PubMed: 24300437]
 19. Niinkoski H, Jula A, Viikari J, Ronnemaa T, Heino P, Lagstrom H, Jokinen E, Simell O. Blood pressure is lower in children and adolescents with a low-saturated-fat diet since infancy: the special turku coronary risk factor intervention project. *Hypertension*. 2009; 53:918–924. [PubMed: 19364991]
 20. American Heart Association Dietary Recommendations for Healthy Children. [Accessed on: January 11, 2015] http://www.heart.org/HEARTORG/GettingHealthy/Dietary-Recommendations-for-Healthy-Children_UCM_303886_Article.jsp

Table 1
Three primordial prevention trials with adolescent blood pressure outcomes

	STRIP	Sodium restriction trial	PROBIT
Country, year study initiated	Finland, 1990	Netherlands, 1980	Belarus, 1996
Intervention period	Infancy through adolescence	Infancy	Infancy
Intervention focus	Counseling on healthful fats, + more fruit/veg/whole grains, less sodium	Provision of lower-sodium formula and baby foods	Breastfeeding promotion
Randomization	Individual	Individual	Cluster
Initial sample size	1062	466	17,046 (31 clusters)
Follow-up age	7 m to 15 y	15 y	11.5 y
Follow-up rate	68% at 6 y 49% at 15 y	38%	80%
Effect on systolic BP, Intervention v. Control, mm Hg (95% CI)	-1.0 (-1.7 to -0.2)	-3.6 (-6.6 to -0.5)	1.0 (-1.1 to 3.1)

STRIP, Special Turku Coronary Risk Factor Intervention Project for Children

PROBIT, Promotion of Breastfeeding Intervention Trial