Primordial Prevention of Cardiovascular Disease

Running title: Gillman; Primordial Prevention of Cardiovascular Disease

Matthew W. Gillman, MD, SM

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

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
Tel: 617-509-9968
Fax: 617-859-9853
E-mail: Matthew_gillman@hms.harvard.edu


Key words: primordial prevention, intervention studies, ideal cardiovascular health, life course, developmental origins, Editorial, blood pressure, metabolic syndrome
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. 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. 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. In cross-sectional NHANES data, this apparent pattern of declining prevalence of ideal cardiovascular health with age continues from adolescence through adulthood.

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. 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.

Many animal experiments suggest that the critical period mechanism is at play in the origins of adult cardio-metabolic outcomes. 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 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. 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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). 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). 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).

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. 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.

**Funding Sources:** This work was funded in part by a grant from the US National Institutes of Health (R37 HD 034568).

**Conflict of Disclosures:** Dr. Gillman receives royalties from Cambridge University Press as co-editor of book titled *Maternal Obesity* and from UpToDate as author of the chapter on dietary fat.
References:


11. Magnussen CG, Niinikoski H, Juonala M, Kivimaki M, Ronnemaa T, Viikari JS, Simell O,


Table 1. Three primordial prevention trials with adolescent blood pressure outcomes.

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

STRIP, Special Turku Coronary Risk Factor Intervention Project for Children
PROBIT, Promotion of Breastfeeding Intervention Trial
Primordial Prevention of Cardiovascular Disease
Matthew W. Gillman

_Circulation_, published online January 20, 2015; 
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231  
Copyright © 2015 American Heart Association, Inc. All rights reserved.  
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at: 
http://circ.ahajournals.org/content/early/2015/01/20/CIRCULATIONAHA.115.014849

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.  
Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: 
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at: 
http://circ.ahajournals.org/subscriptions/