CHILDHOOD PRECURSORS OF ADULT DISEASE:
REVIEW OF THE EVIDENCE FOR DIETARY INTERVENTION

May 1999

Prepared for
Mathematica Policy Research, Inc.
P.O. Box 2393
Princeton, New Jersey 08543

under
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WIC GENERAL ANALYSIS PROJECT, TASK #4
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Food and Nutrition Service
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United States Department of Agriculture
Food and Nutrition Service

prepared by

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FOREWORD

The Life Sciences Research Office (LSRO), an office of the American Society for Nutritional Sciences (ASNS), provides scientific assessments of topics in the biomedical sciences. This report is the product of a project developed at the request of Mathematica Policy Research, Inc. to provide for the Food and Nutrition Service of the United States Department of Agriculture (USDA) a brief summary report containing a critical review of the available data on childhood precursors of chronic disease and of the evidence to support dietary interventions in children two years of age and older. To accomplish this task, the LSRO prepared a summary report outlining the key issues and findings of selected studies that have addressed these questions as they pertain to the five major public issues identified by the USDA, i.e., obesity, cardiovascular disease, cancer, adult-onset non-insulin dependent diabetes mellitus, and osteoporosis. In addition to the summary report, the LSRO prepared tables containing summaries of selected key studies covered in each section of the summary report.

The LSRO is responsible for the report’s contents, conclusions, and overall accuracy. The final report was reviewed and approved by the LSRO Scientific Advisory Committee. Upon completion of this review, the report was approved and transmitted to the USDA. This report does not necessarily reflect the views of members of the LSRO Scientific Advisory Committee or of individual ASNS members.

June 11, 1999

Date

[Signature]

Director
Life Sciences Research Office
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EXECUTIVE SUMMARY

The Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences (ASNS) was asked by Mathematica Policy Research, Inc. to provide for the Food and Nutrition Service (FNS) of the United States Department of Agriculture (USDA) a brief summary report containing an overview of the available data to address the relationship between childhood diet and adult disease. In response, the LSRO has prepared a summary report outlining the key issues and findings of selected studies that have addressed these questions as they pertain to the five major public issues identified, i.e., obesity, cardiovascular disease (CVD), cancer, osteoporosis, adult-onset non-insulin dependent diabetes mellitus (NIDDM). In addition, the LSRO has prepared tables containing summaries of key selected studies covered in each section of the summary report.

A. INTRODUCTION

Diet and nutrition play important roles in the morbidity and mortality associated with many of the chronic diseases of adulthood. Much of the public health agenda of recent years has been devoted to gaining an appreciation of the optimal timing of interventions to reduce the frequency and severity of these conditions. During the course of this quest, many have begun to advocate the application to children of what we have learned about the use of nutrition as a prophylaxis against disease in adults. In order to evaluate the efficacy of this approach, it is necessary to confirm several key associations in the diet-disease relationship as they relate to dietary patterns in children. Among the questions to be addressed are:

- Do the predictors of disease identified in adults (e.g., obesity, hyperlipidemias, hypertension) appear in children, and if so, do they “track,” i.e., are they maintained through to adulthood with the same associated risk? For example, does an obese child become an obese adult at the same risk of disease?

- How do the needs of children for growth and development impact on the relationship between dietary risk factors and disease? How might the needs of children influence the risk/benefit relationship for a given nutrient/disease association? For example, do the increased demands for specific nutrients in childhood obviate the concerns raised by high intakes of these nutrient is adults? Might the reduction of one nutrient have a negative impact on the intake of other nutrients essential to the growth and development of children?

In addition to these core questions which can be applied to any given disease, is the generic question that bears on our ability to address the linkage of childhood diet to adult disease: Are the eating patterns established in childhood maintained through to adulthood?

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1 This Executive Summary represents a synopsis of the material covered in the larger report. For the sake of brevity most of the reference materials used to support these statements have been removed from this document. Consequently, the reader is encouraged to refer to the larger report for fuller documentation and support of the statements contains in this summary.

2 The selection of the studies included in this report was based on the best judgement of the LSRO scientific staff regarding relevance of the studies to the questions in the scope of work. The LSRO summary reports are not intended to be comprehensive but rather are designed to give the contractor a representative overview of the current state of knowledge about the relationship between dietary patterns in childhood and adult chronic diseases.
B. TRACKING OF DIETARY INTAKE

Irrespective of the presumed diet/disease association, the relevance to children of knowledge gained in adults about the efficacy of dietary intervention is contingent on evidence that interventions in children are effective and can be maintained through to adulthood. If childhood dietary habits continue unabated through to adulthood, then early intervention becomes a meaningful option. If, however, these high-risk behaviors do not always begin in infancy/childhood or do not necessarily continue through to adulthood, then the question becomes at what age does the association between a particular diet pattern or nutrient and a disease become significant?

Whether children’s dietary patterns continue into adulthood, i.e., track, is a generic question that provides the basis for discussion of childhood interventions. A substantial body of literature exists with regard to those factors that influence the development of dietary habits in children and has been recently reviewed (Life Sciences Research Office, 1999).

1. Methodology

Variability associated with the use of the various available methods for assessing dietary intake has been the subject of numerous reports. Among the sources of variability associated with these methods are within-individual day-to-day variability, gender, temporal issues (for example, the day of the week; weekday versus weekend, number of days collected, consecutive versus random sampling, and time of the year), measurement error, accuracy of nutrient databases, factors that affect memory (an important issue as most of the diet data are based on individual recall of past intake).

Although these factors are of concern in the design and interpretation of any epidemiological study focused on the diet and disease relationship, many are even more important in the assessment of dietary habits of infants and children. Suggested solutions to these problems are discussed in detail in the body of this report (Chapter 2).

2. Conclusions

Despite the methodological issues discussed above and other limitations pointed out in the review, the selected studies indicate a pattern of dietary tracking that may begin as early as three years of age. As seen in Table 1, a number of studies have been designed to address the specific question of tracking of dietary intake with varying results. A significant limitation of these studies is the small number of diet records collected from the subjects, often either single 24 hour recall or food frequency questionnaires. It has been reported that upwards of 28 days of diet records need to be collected in order to control for intra- and inter-individual variation in intakes of specific nutrients.

C. OBESITY

Overweight in childhood and adolescence has become an important public health issue because of concerns that overweight children and adolescents become overweight adults at increased risk for adverse health outcomes. The role of excessive body weight and body fat in increased mortality and morbidity from CVD, some forms of cancer, diabetes, and digestive diseases has driven much of the national diet and health care agenda (National Research Council [NRC], 1989; U.S. Department of Health and Human Services, 1988).
An extended discussion of the key issues to be considered in the interpretation of data on obesity in children can be found in Chapter 3. Briefly, these issues are the definition of obesity and methods used for its measurement.

1. Epidemiology

From national survey data, the following patterns have emerged in the United States.

   a. Children 5-12 years old

   - Based on analysis of the data from NHANES III 1988-94, approximately 14% of children between 6 and 11 years of age were overweight, using the 95th percentile\(^3\) BMI cutoff points.

   - Based on an analysis of a subset of the NHANES III database, i.e., Phase 1 (1988 to 1991), overweight prevalence for children 6-11 years of age was 11% using the 95th percentile BMI cutoff and 22% based using the 85th percentile of BMI.

   - Prevalence rates were higher among Mexican-American and non-Hispanic black children than among non-Hispanic white children.

   - Comparisons of NHANES III Phase 1 data with earlier surveys have indicated that overweight prevalence (based on 85th and 95th percentiles for BMI) among children aged 6-11 years has increased, with the largest increases occurring since NHANES II.

   - Overall, increases in overweight prevalence between NHANES II and NHANES III, Phase 1 were greater for black children than for white children.

   - Findings from the entire NHANES III 1988-1994 indicated generally higher overweight prevalence rates than those from NHANES III, Phase 1 alone, suggesting that the prevalence of overweight among American children has continued to increase.

   - Weight increases occurred in both sexes and across all racial and ethnic groups.

   b. Adolescents 12-20 years old

   - According to the most recent estimates from NHANES III 1988-94, almost 12% of adolescents 12-17 years of age were overweight using the 95th percentile BMI cutoff points

   - Overweight prevalence was similar among males and females

   - Higher prevalence rates have been reported among Non-Hispanic black and Mexican American adolescents than non-Hispanic white adolescents.

\(^3\) The 85th and 95th percentiles for BMI used to define relative obesity were estimated from National Health Examination Survey (NHES) II (for children 6-11 y) and III (for children 12-17 y).
• In an analysis of NHANES III 1998-91 data using the 95th percentile BMI cutoff, 11% of adolescents 12-17 years of age were overweight across race and ethnic groups.

• When overweight was estimated with the 85th percentile of BMI, the prevalence of overweight was 22%.

• Mexican American males had a higher overweight prevalence than non-Hispanic white and black males.

• Non-Hispanic black females had a higher prevalence of overweight than Mexican-American and non-Hispanic white females.

• The prevalence of overweight among U.S. adolescents is continuing to increase. Analysis of the complete NHANES III 1988-94 data set indicates generally higher overweight prevalence rates than those found in NHANES III, Phase 1.

• Increases in overweight prevalence were apparent among males and females across all racial/ethnic groups.

• It has been reported that U.S. adolescents have become increasingly overweight since the mid 1960s, with the greatest increases occurring between NHANES II 1976-80 and NHANES III 1988-91. During this time, age-adjusted prevalence rates were higher for black adolescents than for white adolescents using the 85th and 95th percentile cutoffs. With the 95th percentile cutoff, the increase in overweight prevalence was highest among white males (from 5% to 14%) across sex/race groups, and with the 85th percentile cutoff, it was highest among black females (from 18% to 30%).

2. **Do obese children become obese adults? Tracking**

Upon review of the most recent studies of the relationship between obesity in childhood and subsequent obesity in adults, the answer is an equivocal yes. Aside from methodological inconsistencies, e.g., standards for defining obesity and measures used to determine body composition, the equivocation derives from the fact that the association between childhood and adulthood obesity becomes stronger as the children grow older. From the limited data available on young children, it appears that risk for obesity as an adult is relatively small particularly in overweight children whose parents are not obese. However, the risk rises as the child grows older, so that those obese children older than ten have an increased risk of becoming obese adults, and that risk is magnified if at least one of the child’s parents are obese.

3. **Dietary factors**

It has been suggested that the increasing prevalence of excess weight and body fat among U.S. children and adolescents reflects a population shift toward positive energy balance in which energy intake exceeds energy expenditure. Although the reasons for this shift may be difficult to explain, data from national dietary intake surveys indicate that increases in energy intake alone do not explain the increase in overweight prevalence. The increase in the prevalence of overweight among children and adolescents may be more a result of a decrease in physical activity than an increase in energy input. The following patterns have emerged that may be relevant to the increase in obesity in children:
• Consumption of fast foods and other away-from-home foods by children and adolescents is frequent and increasing.

• Away-from-home eating is associated with higher energy, fat, and saturated-fat intake than at-home eating.

• Contemporary children and adolescents may be more sedentary than those of previous years, leading to increased prevalence of excessive positive energy balances.

• Overweight in adolescence has been associated with a higher risk of overweight in adulthood and may increase the risk of adverse health outcomes later in life. The risk that an overweight child will remain overweight as an adult increases with age. The predictive value for overweight during adulthood is excellent for an 18-year-old who is overweight and is good for an overweight 13-year-old.

4. Genetics or environment

Although considerable evidence exists attesting to the increased risk for obesity associated with having obese parents, the heritability of obesity and its concomitants, e.g., body type, fat distribution, metabolism, remain to be fully elucidated. Although genetics clearly is an important factor associated with obesity within families, not all obese children have obese parents, and not all children of obese parents are obese. Other environmental based predictors of adult obesity that have been studied include:

• Low socioeconomic status (SES) of a child’s parents and school failure in childhood. Obesity in early adulthood has been associated with low SES, poor physical health, smoking, and alcohol use in adolescence. When these factors were controlled, a relationship was found between early adulthood obesity and adolescent conduct disorders characterized by recurrent impulsive aggression.

• Various psychological variables are associated with adolescent obesity, including emotional disorders, psychopathologies, and troubled parent-child dynamics.

• In families where food is abundant and physical activity is not encouraged, overweight can result without specific psychological or physiological origins.

Clearly, the increasing prevalence of obesity, particularly during adolescence, is a critical concern for the health of the American people. The study of obesity, its causes, and antecedents must remain a high priority as the answers we find to these questions will go a long way towards addressing many of the most pressing issues facing those who must create and steer the American public health agenda.

5. Does childhood obesity increase the risk for adult disease?

Obesity has been associated with increased rates of all-cause morbidity and mortality in adults. Despite inconsistencies in methodology (e.g., use of different standards for defining obesity) and design (e.g., longitudinal versus case-control), the evidence supports the contention that the risk for all-cause morbidity and mortality in adults is greater for obese children, particularly post-pubescent children. Minimal risk has been associated with obesity in younger children or infants. Of the studies done to date, it appears that childhood obesity especially in older children is an independent risk factor for adult morbidity and mortality. On the basis of the studies reviewed, obesity in childhood has been linked to risk factors for numerous diseases of adulthood.
However, the role of diet per se in this relationship is unclear as, dietary factors were not included in the majority of the studies designed to evaluate these relationships.

D. CANCER

1. Childhood diet as an independent risk factor for site-specific cancers

The majority of studies intended to focus on this question have involved retrospective comparisons of diets of groups who have cancer and age-matched groups who are not ill, i.e., case-control studies. Inferences may be drawn about potential associations between diet and site-specific cancers. However, it is not possible from these types of studies to determine either cause-and-effect or at what point an increase in specific types of foods or the amounts of putative active substances, e.g., vitamins and/or other micro-nutrients might be beneficial.

Several groups of investigators have focused on the potential relationship between childhood/adolescent lifestyle, e.g., dietary habits and exercise, and risk of site-specific cancers. The utility of such studies is enhanced by knowledge of specific biomarkers and/or risk factors that emerge during specific developmental periods. The best example is breast cancer, which is associated with several diet sensitive risk factors including delayed age at menarche, low body weight during adolescence, and greater height. Several studies have been designed to assess the impact of diet on these risk factors (Table 4). For example, one study included an examination of diet (vegetarian versus non-vegetarian) and hormone levels in adolescent girls. Another studied the relationship between dietary factors (total fat, categories of fat, total energy) on age of onset of menarche.

Some case-control studies have focused on the potential risk associated with certain diets without addressing specific biomarkers of breast cancer. One group of investigators used an "ecological study" of the relationship between lifestyle changes that were imposed on adolescent girls during World War II, to make inferences about the relationship between these changes (including diet) and subsequent development of breast cancer.

In many of the studies intended to test hypothesized diet and disease relationships, methodological inconsistencies have resulted in confusing and conflicting results. For example, one study reported a positive association between risk of breast cancer and intake of high fiber foods, specifically fruits and vegetables. These investigators speculated that the effect was due to increased intakes of β-carotene. By contrast, another group reported the exact opposite effect, i.e., a significant inverse relationship between intake of carotene-rich foods and risk, in women who had a family history of breast cancer. Diet data in both studies were retrospective, referenced to two years prior to study in one and to adolescence in the other. In neither case were total consumption of individual nutrients actually assessed. In one of the studies, carotene intake was estimated based on “reported frequency of consuming servings of cooked and raw carrots and cooked and raw spinach 2 years before the interview.” The relationship was even more tenuous in the other report in which only intake of high fiber foods, subsequently divided into fruits and vegetables and starchy foods was estimated.

The majority of studies of the diet/cancer relationship have focused on food groups specifically food groups that have been associated with adult disease, such as high fat foods. Consequently, no data are available on the intake of total energy or specific nutrients that could be used to evaluate either tracking or an independent association between childhood intake and site-specific cancer in adults. Moreover, because of the nature of the analyses, i.e., generation of associated risks, what data were collected on diet were not evaluated in such a way as to be able to make inferences about tracking of these intake patterns from childhood to adulthood.
2. **Childhood obesity as an independent risk factor**

BMI has been identified as a risk factor for numerous site-specific cancers, e.g., colon cancer, breast cancer. As documented in Table 4, a number of studies have included BMI in an attempt to ascertain childhood antecedents of site-specific cancers with varying results. Positive associations were reported between BMI in adolescence (but not in adults) and risk for gastric cancer and breast cancer. In one report, no association could be found between either adolescent or adult BMI and prostate cancer. In another report, larger BMI was found to significantly accelerate the occurrence of menarche, which would be associated with a decreased risk of breast cancer. However, it has been suggested that the protective effect associated with obesity-related early onset of menarche is “temporary and small, compared to the risk of increased promotion of carcinogenesis when obesity continues after the teenage years.”

The often conflicting data on the relationship between body size and breast cancer was summarized as follows: “the contrasting effects of body size on pre-menopausal breast cancer compared with postmenopausal breast cancer and the lack of a strong association between body mass and postmenopausal breast cancer in some cohort studies has led to a view that obesity has little influence on breast cancer risk...Recent research suggests that, compared to body mass indices, adult weight gain and increased central body fat may be more specific markers of the metabolic consequences of obesity and therefore may predict health outcomes more consistently... Data on lifelong weight changes and the location of fat depots may more precisely identify women with high risk patterns...” As reinforced by several investigators, in addition to focusing on distribution of body fat, future research will need to assess more directly the relationship between specific timing of weight gain, energy balance, activity levels, and known risk factors, e.g., steroid hormone levels, in order to predict more accurately when and in whom breast cancer risk is affected.

Because many investigators have reported positive associations between BMI and various site-specific cancers, it is logical to assume that energy intake would also be considered a potential risk factor. In the studies reviewed in Table 4 that attempted to address childhood precursors of adult cancer, only two, contained specific data on nutrient consumption. However, in contrast to the majority of studies reviewed, the intention of these two studies was to assess prospectively the impact of diet on specific risk factors for breast cancer, i.e., hormone concentrations and age at menarche. Neither tested the possibility of tracking of the relationships being tested or the diet/outcome relationship in adults.

3. **Summary and conclusions**

Much of the knowledge of the relationship between diet and cancer in humans has been provided by population-based epidemiological studies. However, because of the lack of either specific traceable biomarkers and prospective data beginning in childhood, it is not possible to determine at what point this association might begin or when a prophylactic intervention might be appropriate. Furthermore, because none of the case-control population-based studies reviewed included analysis of individual nutrients, it is only possible to make general inferences based on food groups about potential diet/cancer links. Finally, because of the nature of the analyses performed in studies done to date, it is not possible to determine whether the intakes of suspected foods or food groups track from diets of children to those of adults.

In addition to all the problems associated with case-control or population-based epidemiological studies, a specific issue in those studies that have addressed the BMI relationship has been the absence of attempts to corroborate retrospective recall anthropometric data by reference to medical records. Further, none of the studies reviewed included a working definition of obesity, and most used the control sample rather than the
general population as the reference standard. The assumption is that the sample is representative of the population.

Based on the extant data about the tracking of obesity, i.e., the later obesity occurs, the more likely it is to track and have health consequence (see Chapter 3), interventions would seem to be better focused at population-based efforts to stem the increase in post-adolescent obesity in both individuals and the general population.

E. CARDIOVASCULAR DISEASE (CVD)

Risk factors that have been identified as predictors of adult CVD disease include: age, gender (males are at higher risk than females), family history, high concentrations of total serum cholesterol (TC) and low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL), a high LDL:HDL ratio, smoking, hypertension, obesity, and diabetes. Many of these risk factors have been linked to characteristic dietary patterns in adults and consequently much attention has been paid to interventions aimed at changing these patterns. Few data have been available on the time course of CVD vis-à-vis the diet and risk factor relationship. Several longitudinal studies have been conducted that have included an exploration of the emergence of these risk factors and their relationship to the development of adult disease. The following sections will include presentations of those data that have been used to address the association between the appearance of risk factors in children and the development of CVD in adults.

1. Do adult risk factors/biomarkers appear in children?

Based on the studies reviewed in Table 5a, evidence exists to support the notion that risk factors associated with adult CVD appear in children. Racial, gender and familial differences have all been associated with patterns of adverse risk factors in children. However, inconsistencies have been reported relative to individual risk factors. Specifically, levels of total cholesterol in children have not been consistently associated with risk in young adults. The most consistent factor associated with adverse CVD risk in both children and adults has been BMI. Other risk factors indicative of adverse risk such as the circulating lipoprotein pattern (high LDL and low HDL) have been consistently reported. The prevalence, extent and nature of lesions in vasculature of young accident victims examined at autopsy have been described in several studies. Associations have been made between the extent and nature of these lesions and known risk factors such as circulating lipoprotein concentrations and BMI.

None of the studies reviewed in Table 5a included any data in the analyses on the relationship between the risk factors identified in children and adolescents and other environmental factors, including diet. Moreover, with the possible exception of excess weight gain/obesity, there are few data regarding risk factor levels in young prepubescent children. Consequently, although the evidence suggests that risk factors for CVD appear in children and adolescents, the link between diet and these risk factors can only be inferred from our understanding of the diet/CVD link in adults. Because of the absence of any data on these relationship, there appears to be little justification for dietary interventions in young children at this time.

2. Tracking of CVD risk factors

Table 5b includes summaries of studies that have been designed to address specifically the issue of tracking of CVD risk factors from childhood to adults. As with those studies that have confirmed the presence of adverse levels of risk factors in children, the tracking studies suffer from inconsistencies in the results that
could be accounted for by design, sample characteristics, differences in analytical technique occurring between and within studies, and differences in criteria used to define “adversity.” It does appear from the studies reviewed that temporal patterns exist with regard to most of the risk factors studied.

There has been mixed success with regard to the utility of employing childhood levels of risk factors as predictors of adult levels. For example, using data collected during the Bogalusa Heart Study, adverse levels of LDL-C (based on national standards for adversity established by the National Cholesterol Education Program) were shown to persist from childhood to young adult life. In another report from the Bogalusa study group, “clustering” of risk factors (serum TC, systolic blood pressure [SBP], and BMI) was shown to have limited utility in predicting adverse levels in adults. In contrast, investigators involved in the Muscateine study reported that TC was not a good predictor of those who would require interventions as adults. Of the children who had TC levels exceeding 75th percentile of the NCEP standard, 75% of girls and 56% of boys did not qualify for interventions as adults.

No consistent pattern has emerged. In fact, variables such as childhood levels of total cholesterol and HDL-C have not been statistically correlated with adult levels in several reports. Although the evidence derived from such studies as the Bogalusa Heart Study and the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) Study (discussed in detail in Chapter 5) provide much useful insight into the pathogenesis of atherosclerosis and CVD, none of that evidence was directly linked to diet. Again, the relationship between diet and the onset of aberrant risk factors in children is implied by evidence linking risk factors in adults, such as elevated serum cholesterol, aberrant lipoprotein profiles, to diet.

Of the studies reviewed, the only study conducted in children and young adults that included data specifically collected to assess the long-term relationship between diet and CVD risk factors was the Amsterdam Growth and Health Study. The results from this study raise more questions than they answer. For instance, in one study by the Amsterdam group, a negative association was reported between body weight and energy intake. Another reported “no relationship” between the dietary intake of macronutrients and CVD risk factors.

In summary, although evidence suggests that many of those factors that have been associated with adult CVD appear in children and adolescent, the utility of monitoring the levels of many of these factors in children, particularly young prepubescent children, in order to predict individuals at risk for adult disease has not been firmly established. An additional consideration is the potential for adverse outcomes consequent to labeling young children as high risk based on such screening practices. Moreover, in light of the absence of many of the other variables that may influence these risk factors, such as diet, family history, demographics, in the analyses presented it would appear to be premature to commit to this practice at this time.

3. **Hypertension**

The importance of hypertension to the pathogenesis of CVD disease and particularly atherosclerosis is evidenced by the findings of the PDAY investigators who observed “hypertension augments atherosclerosis in both men and women primarily by acceleration of the conversion of fatty streaks to raised lesions beginning in the third decade of life, and the effect of hypertension increases with age.” Clearly, the question is in whom is this risk most apparent and can we predict this risk based on measurement of BP in children? Based on the review of the studies in Table 5c, the answer to this latter question is maybe.

Although the majority of the studies reviewed examined temporal associations between BP and other risk factors in youth and into adulthood, few actually focused on clinically diagnosed essential hypertension.
Several studies including the Bogalusa Heart, the Muscatine Iowa, and the PDAY studies have been designed to provide evidence of tracking of BP and most results are indicative of a predictive value particularly for systolic blood pressure (SBP). However, other studies, such as the Tecumseh, Michigan study are less supportive of the use of childhood BP to predict adult risk. The most important finding of the Tecumseh study is supportive of the majority of studies investigating the link between BP and other risk CVD risk factors, i.e., that body size and family history are perhaps the most important factors related to clinically adverse levels of BP. Race and gender have also been consistently identified as playing important roles in the identification of whom might be at risk.

Few studies have addressed the potential link between diet and nutrient intake and BP in children. Data from the Sodium-Potassium Blood Pressure Trial in Children are indicative of a relationship between circulating levels of specific fractions of calcium; however, no association with dietary intake was observed in this cohort. In contrast, the investigators in the Dietary Intervention Study in Children (DISC) study, Simons-Morton et al. (1997), reported significant inverse associations between dietary intake of micronutrients (calcium, magnesium, potassium and protein) and BP, and positive association with fats in a selected sample of children with high levels of LDL-C.

Again, although some of the available evidence indicate a long-term pattern of BP, the relationship of this pattern to factors that might be considered in an dietary intervention in children is not clear at this time.

4. Obesity

As seen in Table 5d, BMI which is used as the default marker for adiposity, has been strongly, consistently, and independently associated with adverse CVD risk during childhood, over the course of development to adulthood, and in adults. In addition to associations with pathological lesions of coronary vasculature, BMI has been linked to the primary biochemical CVD risk factors, i.e., elevated LDL-C and reduced HDL-C. Perhaps more importantly than absolute BMI at a given point in time, an even greater concern may be the pattern on weight gain over time. As demonstrated in the report of the Minnesota Children’s Blood Pressure Study, weight gain through childhood to adulthood may be a more significant predictor of risk than a single measure of weight. Consequently, prevention of excess weight gain rather than weight loss might be a more effective intervention strategy.

The importance of weight gain was emphasized in several reports reviewed, including the Bogalusa Heart Study, in which the significant association between secular trends in weight gain and CVD risk factors was demonstrated. Again, as noted for all of the other aspects of the relationship between childhood antecedents of adult CVD, the absence of any data with regard to the role of diet in the development and maintenance of adverse levels of BMI, makes discussion of specific dietary interventions in children premature. Furthermore, the question of the type, (weight loss versus prevention of excess weight gain), and timing, (pre-or post-adolescence), of such intervention remains unresolved.

5. Impact of interventions to reduce CVD risk in children

Despite the vast amount of evidence linking adult dietary patterns to risk factors for adult CVD, there remains little but inference to support dietary interventions in children. Yet, the desire to protect children from the onset of these disabling diseases has driven much of the debate in the national nutrition policy arena. Based on reports of adverse effects consequent to the unsupervised implementation of diets intended to reduce CVD risk factors in children, the safety of such interventions has become a focal point of concern. Consequently, a
number of studies have been designed to address the safety and efficacy of dietary interventions in children and are summarized in Table 5e.

The largest trial designed specifically to address the safety and efficacy of an intervention for the reduction of a putative CVD risk factor in children has been the Dietary Intervention Study in Children (DISC). The objective of this multi-center prospective intervention trial was to "assess the efficacy and safety of a lipid-lowering diet in 8 to 10-year old children with moderately elevated LDL-C." The study involved a total of 663 children divided into an intervention group (n=334) and a usual care or control group (n=329). The groups were matched at baseline for gender, age, mean LDL-C, normal dietary intake, anthropometric measures (height, weight, BMI, and skinfold thickness from three sites), and BP. The DISC Research Group (DISC Collaborative Research Group [The Writing Group], 1995) reported a modest difference in the decrease in LDL-C between the two groups in the absence of any differences in growth or serum ferritin (the other major dependent variable). This study also provided confirmation of other reports of the developmental changes in LDL-C levels. As stated in the conclusions of one of the DISC reports, in pubertal children, sexual maturation, BMI, dietary interventions (in girls), and dietary cholesterol (in boys) were significant determinants of LDL-C. "Sexual maturation was the factor associated with the greatest difference in LDL-C."

It should be noted that the use of low fat diets was not without consequence. Lower fat intake was associated with higher levels of red blood cell folate and hemoglobin, higher intakes of folate, vitamin C, and vitamin A, lower intakes of calcium, zinc, magnesium, phosphorus, vitamin B12, thiamin, niacin, and riboflavin, increased risk of consuming less than 2/3 of the RDA (National Research Council, 1989) in girls at baseline, and zinc and vitamin E in both genders at all visits. Given the extent and nature of these dietary findings, it would appear that the study could have benefitted from an analysis of foods in addition to the individual nutrient assessments. Such an analysis might have shed light on which foods contributed to these effects and allowed for a more effective evaluation of the efficacy of this and subsequent interventions.

The finding of increased risk for reduced calcium intake is particularly disturbing and has been reinforced by the reports in which reduced calcium intake in children consuming low versus high fat diets have been reported based on analysis of national survey data. The risk for lower intakes of several essential nutrients including calcium was dismissed by the DISC investigators because "no adverse effects were observed on blood biochemical measures of nutritional status." However, no biochemical assessments of vitamin B12, thiamin, niacin, or riboflavin were performed. Further, there were no assessments of bone density or any other measures of bone health that are critical in the evaluation of the impact of dietary calcium, a significant issue particularly in adolescent girls (see Chapter 7 of this report). Finally, as reviewed in Table 5c, another report from the DISC group included findings of significant inverse associations between dietary intake of several nutrients (calcium, magnesium, potassium and protein) and BP, adding additional concern with regard to the potential harm from reduced intakes of these essential nutrients.

Several other studies have been conducted to evaluate the impact of dietary interventions in children. The Child and Adolescent Trial for Cardiovascular Health risk (CATCH) study involved a comparison of three treatments: an intense school-based education diet and health intervention plus physical education (the CATCH intervention), the CATCH intervention plus home-based education program, and a control group of students receiving the standard school-based health education curriculum. A total of 96 elementary schools participated in this study. Subjects were randomized into the three treatment groups (total n = 7,795; mean age at baseline 8.75 y). The dependent variables in this study were psycho-social factors which "...influence behavioral risk factors (dietary, physical activity, smoking) which influence physiological risk factors (blood lipids and blood pressure) which determine morbidity and mortality." These investigators reported "sustained significant effects
in improved knowledge, intentions, self-efficacy, usual behavior, and perceived social reinforcement for healthy food choices after three years.” These authors concluded that “The CATCH program was effective in changing the psychosocial variables likely to influence a reduction in behavior for CVD.” None of the endpoint risk factors (e.g., blood lipids) or actual dietary intake were included in this report.

Other groups have reported no adverse effects from dietary interventions specifically designed to reduce levels of putative risk factors in children and have concluded that no safety concerns exist with regard to these treatments (Table 5e). In one study, the intervention, the NCEP Step 1, (total fat intake less than 30% total calories, less than 10% saturated fat, and 100 mg cholesterol/1000 kcal/day) was successfully implemented in a “convenience” cohort of 138 children ranging in age from 2 to 15 years. After three years, TC was significantly reduced compared to baseline levels. However, a number of issues place limitations on the interpretation and generalizability of these results.

- This was an unblinded observational study of a self-selected “convenience sample” without the benefit of a comparison group. The authors acknowledged that “the study group was a sample of convenience, reviewed retrospectively by chart audit, and thus was not randomly selected or population based. Combining patients from three sites poses problems with comparability of methods and data.”

- Dietary intake data, either at baseline or at any point of the intervention, were not presented, discussed, or included in the analyses. The authors’ use of the dependent variable, TC, to establish compliance might have been tested by evaluating the diets of these subjects.

- No analysis or control for gender or age was included in these data. There was an apparent interaction with age as evidenced by the larger changes in lipid profiles occurring in older children (>10 y). The pattern of change were consistent with those age-dependent changes described in previous studies (Srinivasan et al., 1995).

Based on these limitations, the authors reserve in restricting their conclusion about the safety of this intervention to “no demonstrable adverse effect on growth,” was clearly appropriate.

A similar intervention study was conducted in which growth as reflected by changes between treatment groups over a three-year period was assessed in 261 hypercholesterolemic (TC greater than 176 mg/dL; 75th percentile) children between the ages of 3.9 and 9.9 years. After initial TC screening, candidate subsequently evaluated for LDL-C concentrations. Those meeting the study criteria (LDL-C 107 to 164 mg/dL for boys, 112 to 164 mg/dL for girls) were randomized into three study groups: 2 nutrition education interventions and an “at-risk” control group. An additional “not-at-risk” control group was selected from children without elevated TC (less than the 60th percentile). Anthropometric measures (height, weight, 4 sites for skinfold measurement), BP, and TC were measured at 3, 6, and 12 months after initiation of the interventions. Three 24-hour diet recall (2 weekdays and 1 weekend day) were collected at each evaluation. The dependent variables did not include changes in blood lipids. Again, the intervention resulted in significant reduction intake of total and saturated fat, without an untoward impact on linear growth. However, not only was there no data or analysis on the efficacy of the intervention in terms of reduction of the putative risk factor (TC or LDL-C), there were no assessments of other nutrients that might have been negatively affected by this intervention. Consequently, while confirming a lack of a linear growth effect, this study was not designed to test efficacy or to rule out the potential for other adverse dietary and nutritional effects.
In conclusion, while the efficacy of educational interventions has been confirmed in several reports, safety concerns remain. We know that we can reduce the levels of putative CVD risk factors in children, the more important unanswered questions are when and/or whether we should.

F. ADULT ONSET NON-INSULIN-DEPENDENT DIABETES (NIDDM)

1. Background

NIDDM is a series of diseases that share many overlapping sets of symptoms of disturbed glucose homeostasis. It does not require exogenous insulin to prevent death from the immediate metabolic consequences of hypoglycemia. Because of the heterogeneity of etiology, NIDDM cannot be treated as a single entity. NIDDM patients present insulin resistance (i.e., a diminished response to insulin) and pancreatic β-cell dysfunction, along with impaired glucose tolerance.

The development of adult-onset NIDDM has been divided into stages. These stages may occur in overlapping time frames, and in any individual NIDDM may progress through some or all of them. Early stages include:

- Insulin resistance: Disorders of insulin metabolism, insulin signaling, glucose transport, glucose metabolism, energy metabolism or a variety of other metabolic disorders that generally manifest as a decreased responsiveness to insulin. The genetic basis of insulin resistance is known in only a minority of the cases.

- Impaired glucose tolerance: (IGT, defined as blood glucose levels after ingestion of glucose that remain elevated above normal levels but below those levels necessary for a diagnosis of diabetes). This IGT is accompanied by insulin resistance and hyperinsulinemia.

- Diabetes without complications: increased insulin secretion is no longer sufficient to compensate for the insulin resistance and the hyperglycemia worsens to diabetes without complications. NIDDM often remains undiagnosed at this stage. Individuals may take several decades to transverse the first three stages before they progress into the fourth stage.

- Diabetes with vascular or neurological complications: The complications of any form of NIDDM include accelerated coronary artery and peripheral macrovascular disease, microvascular complications, nephropathy, retinopathy, and neuropathy. Improved control of blood glucose levels decreases the rate of progression of the complications

NIDDM accounts for approximately 90% of cases of diabetes. There are marked geographic and ethnic differences in prevalence. Increased prevalence is found in Native Americans, African-Americans, Hispanics,

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4 Although the focus of this review is on childhood antecedents of adult-onset NIDDM, it should be noted that there are number of subtypes of NIDDM occurring in children including maturity-onset diabetes of youth (MODY), various severe insulin resistance syndromes, and early-onset classic NIDDM.
Asian and Pacific Islanders. Females are more frequently affected than males. The prevalence of NIDDM appears to be on the increase in Native American and African-American youth.\(^5\)

2. **Biomarkers and risk factors in adults**

IGT, which represents an inadequate response of compensatory insulin secretion to increased insulin resistance, is probably the most reliable biomarker for NIDDM. A number of subclinical features of the early stages of NIDDM development such as hyperglycemia, elevated glycohemoglobin levels, insulin resistance, and hyperinsulinemia are also used as biomarkers for the disease.

Known risk factors of NIDDM also include high BMI, central or “android” obesity as indicated by an elevated waist-hip ratio, duration of obesity, physical inactivity, and a high-fat diet. There is a strong genetic contribution to NIDDM. Monozygotic twins have a concordance of 70-80% compared with a concordance of 10-20% in dizygotic twins. The lifetime risk of developing NIDDM is 40% in offspring of a diabetic parent compared to the 3% prevalence world-wide. Individuals with close relatives who have NIDDM, women with a history of gestational diabetes, and members of geographic or ethnic populations with a history of high prevalence of NIDDM represent high-risk groups as well. Adult-onset NIDDM may have a different set of risk factors and a different set of outcomes for Native Americans than for populations of Caucasian or Asian descent.

3. **Do adult biomarkers appear in children? Do they track?**

Because NIDDM may take several decades to progress through the stages of development, research has been focused on the earliest identification of markers such as hyperglycemia, insulin resistance, hyperinsulinemia, and central obesity, particularly those that may appear during youth. Some reports, such as the analyses of the Bogalusa Heart Study cohort, have provided support for the tracking of NIDDM risk factors from childhood through young adulthood. Using parental history as a surrogate measure of future risk, the risk factors may track into manifest adult-onset NIDDM. However, even if these markers or other risk factors are present in childhood or adolescence, it is difficult to distinguish them as early indications of adult-onset NIDDM or as indicators of other variants of NIDDM that occur in children and adolescents, especially in minority populations (e.g. early-onset classic NIDDM, MODY, insulin resistance syndromes, etc.).

4. **Dietary links to biomarkers: do they track?**

Because NIDDM and CVD share so many risk factors in common, the dietary antecedents of NIDDM may also be the same as those for CVD. About 60-80% of adult NIDDM patients are obese. Obesity, in particular central or abdominal obesity, and physical inactivity have been shown to be independent risk factors for insulin resistance, hyperinsulinemia and NIDDM. These are robust correlations, supported by the evidence from many independent studies.

In adults, evidence exists to support a linkage between high intake of dietary fat and hyperinsulinemia, insulin resistance, and NIDDM. In addition, increased intake of dietary fiber and decreased dietary glycemic index (a qualitative indicator of carbohydrate’s ability to raise blood glucose level) have been shown to decrease risk

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\(^5\) Recent studies suggest that early-onset classic NIDDM is the most common form in children and adolescents (Glaser, 1997). The noted increased prevalence in Native American and African-American youth refers to early-onset classic NIDDM.
of NIDDM. In adults, decreased dietary energy intake, decreased fat intake, weight loss, loss of abdominal visceral fat, increased fiber intake and increased physical activity have all been shown to prevent or delay insulin resistance, hyperinsulinemia, IGT, and NIDDM.

Although no studies were found that directly linked dietary intake in children to adult-onset NIDDM, an indirect measure of this potential association may be found in the link between the growing incidence of obesity in children and the increased incidence of NIDDM in African American and Native-American children. A review of the prevalence and factors associated with the tracking of obesity may be found in Chapter 3.

5. Summary and conclusions

The extensive evidence for the linkage between obesity and physical activity and NIDDM has been well recognized. The goals of a diet and exercise treatment program are to enhance control of glucose levels, decrease insulin resistance, and reduce the acceleration of macrovascular complications. In adults, the short-term benefits of such intervention programs have been well documented, however, long-term compliance has been very difficult to achieve. Poor long-term success of diet programs has led some physicians to become more interested in pharmacologic interventions. Others view this as a rapidly evolving field in which optimum programs have not yet been developed.

The problematic long-term success in adults of diet programs for the prevention and treatment of adult-onset NIDDM and the knowledge that NIDDM is in part, preventable has led to efforts to prevent or delay NIDDM through diet and exercise programs aimed at children. The appeal of intervention in childhood and adolescence includes: for school-based programs the ability to work with a “captive audience” eager to learn new ideas; a controlled environment in which both dietary intake and physical activity can be altered; the opportunity to alter dietary and activity patterns at a time when the patterns are being established; and the potential long-term benefits of decreased risk factors that track into adulthood. As summarized in Table 6b, a number of intervention programs have been attempted in children with mixed success.

G. OSTEOPOROSIS

Osteoporosis in females has been defined as an increased bone fragility and increased risk of fracture as a result of bone mass more than 2.5 standard deviations below the mean for young adult women (Institute of Medicine [IOM], 1997). In the report of the National Institutes of Health (NIH) Consensus Development Conference on Optimal Calcium Intake, several studies were cited in which certain at-risk groups were shown to be in negative calcium balance (losses exceeding intake) despite having intakes that meet or exceed recommended levels.

Women in the first 6-8 years after the onset of menopause have a net negative calcium balance and loss in bone mineral content (BMC) and bone mineral density (BMD), associated with the declining estrogen levels. This loss in BMC and BMD can be slowed but cannot be reversed by increased calcium dietary intake (NIH, 1995). After the period when estrogen deficiency is no longer acute (approximately 10 years after menopause), increased dietary calcium is somewhat more beneficial in slowing bone loss (NIH, 1995). However, for each individual there is a plateau above which increased dietary intake of calcium has no further beneficial impact on BMC or BMD (IOM, 1997).

Other factors including dietary constituents, estrogen replacement, vitamin D supplementation, and exercise have been shown to affect bone loss (IOM, 1997; NIH, 1995). Even when calcium intakes and other factors...
have been optimized to prevent bone loss, osteoporotic post-menopausal women have a net negative calcium balance. Because there are such clear limitations to preventing bone loss by interventions in adults, attention has turned to interventions begun earlier in life, i.e., building calcium reserves through building stronger bones during childhood. The NIH Consensus Development Conference asserted that two factors that influence the occurrence of osteoporosis are optimal peak bone mass attained in the first two to three decades of life and the rate of bone loss in later years (NIH, 1995).

A substantial proportion of children do not meet currently recommended guidelines for calcium intake. Contemporary 6- to 11-yr-old children may even show a decreased calcium intake compared to those measured a decade earlier (NIH, 1995). This latter observation is supported by the data indicating significant declines in calcium intakes over a ten-year period, particularly for adolescent girls aged 15 to 18 years. Moreover, the percentage of adolescent girls who consume less than two thirds of the RDA (NRC, 1989) has been reported to have increased with age reaching 77% of 15 to 18 year old girls evaluated during the period of 1990-1992 (Table 7-2). Concerns about the intakes of adolescents has been reinforced by data collected for the USDA CSFII (1994-1996), documenting that only 36% of males and 14% of females adolescents consumed diets meeting the RDA for calcium.

Of the studies on calcium balance, bone mineralization, and bone strength in children, few have been designed to address tracking and long-term consequences. Fewer still have studied tracking from adolescence to adulthood, the period when peak bone mass is achieved. Such tracking studies have important implications to public health policy because they are designed to identify which groups are at greatest risk due to insufficient intakes and when interventions might be most warranted. Moreover, strategies could be developed to ensure that interventions such as increased dietary intake of calcium, initiated early in life persist over time. One obstacle confronting those that might pursue an examination of the tracking question is that current intake may not be an accurate reflection of past intake.

Studies of calcium supplementation in children have yielded fairly consistent results. In the selected examples in this review, increased daily calcium intake in the form of dairy milk, resulted in significant increases in BMD and BMC for 12 yr-old females, and increased dietary calcium resulted in an increased net calcium balance in 8-15-yr-old females from osteoporotic and non-osteoporotic families. It should be noted, however, that BMD has been shown to decline shortly after acute interventions cease. Thus, acute intervention in children in the absence of long-term strategies for maintaining calcium balance is of unproven benefit.
CHAPTER 1: INTRODUCTION

A. BACKGROUND

Diet and nutrition play important roles in the morbidity and mortality associated with many of the chronic diseases of adulthood. Much of the public health agenda of recent years has been devoted to gaining an appreciation of the optimal timing of interventions to reduce the frequency and severity of these conditions. During the course of this quest, many have begun to advocate the application to children of what we have learned about the use of nutrition as a prophylaxis against disease in adults. In order to evaluate the efficacy of this approach, it is necessary to confirm several key associations in the diet-disease relationship as they relate to dietary patterns in children. Among the questions to be addressed are:

- Do the predictors of disease identified in adults (e.g., obesity, hyperlipidemias, hypertension) appear in children, and if so, do they "track," i.e., are they maintained through to adulthood with the same associated risk? For example, does an obese child become an obese adult at the same risk of disease?

- How do the needs of children for growth and development impact on the relationship between dietary risk factors and disease? How might the needs of children influence the risk/benefit relationship for a given nutrient/disease association? For example, do the increased demands for specific nutrients in childhood obviate the concerns raised by high intakes of these nutrients in adults? Might the reduction of one nutrient have a negative impact on the intake of other nutrients essential to the growth and development of children?

In addition to these core questions which can be applied to any given disease, is the generic question that bears on our ability to address the linkage of childhood diet to adult disease: Are the eating patterns established in childhood maintained through to adulthood?

B. TECHNICAL APPROACH

The Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences (ASNS) was asked by Mathematica Policy Research, Inc. to provide for the Food and Nutrition Service (FNS) of the United States Department of Agriculture (USDA) a brief summary report containing an overview of the available data to address the above questions. To accomplish this task, the LSRO has prepared a summary report outlining the key issues and findings of selected studies that have addressed these questions as they pertain to the six major public issues identified, i.e., obesity, cardiovascular disease (CVD), cancer, osteoporosis, adult-onset non-insulin dependent diabetes mellitus (NIDDM), and diet-related impaired performance. The LSRO has also prepared tables containing summaries of key selected studies covered in each section of the summary report.

The LSRO notes that the selection of studies included in these reports was based on the best judgement of the LSRO scientific staff regarding relevance of the studies to the questions in the scope of work. The LSRO summary reports are not intended to be comprehensive, but rather are designed to give the USDA/FNS a representative overview of the current state of knowledge about the relationship between dietary patterns in childhood and adult chronic diseases.
Figure 1 is a proposed decision-tree approach that might be used to address the state of knowledge with regard to the need for intervention in childhood to address a given diet/disease association. LSRO recognizes that the ability to reach a publicly relevant decision at any point of this decision-making process will be contingent on the willingness of all those involved in conducting and evaluating research, and/or making policy based on the extant science to establish agreed-upon criteria for each contingency. Notwithstanding our appreciation for the difficulties in reaching such decisions, LSRO used these questions to organize a balanced presentation of the key controversies for each of the topics included in the scope of work. The focus was on the adequacy of the extant data to address the generic question of eating patterns in childhood tracking through to adulthood, followed by an examination of the evidence to address the other questions as they pertain to five of the major public health concerns, obesity, cardiovascular disease, adult-onset diabetes, cancer, and osteoporosis.

In addition to the major chronic diseases of adulthood, imbalances in diet and/or nutrient status in childhood can have significant effects on a child’s development and acquisition of requisite skills to interact with their environment during their learning and formative years. These effects can have potentially long-term ramifications for later performance as an adult. Consequently, an example of such relationships will be covered; the impact of iron deficiency on cognitive development.
Figure 1. Decision Tree: Model for Assessing the Role of Children's Diet/Nutrition in Chronic Disease in Adults

Adult Chronic Disease

Are there dietary links to the disease?

Yes

Do biomarkers of the disease appear in children?

Yes

Do the markers track?

Yes

Are there dietary links to the biomarkers?

Yes

Consider intervention:
include potential interactions/safety concerns
(risk/benefit analysis)

No

Not an issue for children

No

Look for other links/causes

No

Investigate relevance of biomarkers to adult conditions

No

Investigate relevance of biomarkers to adult conditions
CHAPTER 2: TRACKING OF DIETARY INTAKE PATTERNS

Irrespective of the presumed diet/disease association, the relevance to children of knowledge gained in adults about the efficacy of dietary intervention is contingent on evidence that interventions in children are effective and can be maintained through to adulthood. If childhood dietary habits continue unabated in adult life, then early intervention becomes a meaningful option. If, however, these high-risk behaviors do not always begin in infancy/childhood or do not always continue through to adulthood, then the question becomes at what age does the association between a particular diet pattern or nutrient and a disease become significant?

Whether children’s dietary patterns continue into adulthood, i.e., track, is a generic question that provides the basis for discussion of childhood interventions. A substantial body of literature exists with regard to those factors that influence the development of dietary habits in children and has been recently reviewed (LSRO, 1999).

A brief discussion of methodological issues relative to dietary tracking is warranted, as these issues will influence the validity of studies of all aspects of the diet/disease relationship.

A. METHODOLOGICAL ISSUES

For several reasons, the reliability of dietary intake data has been questioned as an accurate reflection of long-term intake patterns. For instance, Heaney et al. (1990) evaluated the consistency of intakes of calcium, phosphorus, protein, and energy in two groups of women (total n=329) over periods ranging from six months to 20 years, and observed that “current intake is not a good estimator of past intake for most nutrients...” Moreover, Møller-Jensen et al. (1984) reported that in a study of 34 males and 45 females whose diets were evaluated over a 15- to 25-year period, “...recall of past diet is strongly influenced by present dietary habits.” Consequently, the results of these studies in adults are indicative of a failure of retrospective data to reflect long-term eating patterns accurately.

Variability associated with the use of the various available methods for assessing dietary intake has been the subject of numerous reports (Anderson, 1986; Anonymous, 1991; Beaton et al., 1979; El Lozy, 1983; Guenther et al., 1997; Krall et al., 1988; Quandt, 1987; Sempos et al., 1985; Wu et al., 1986). Among the sources of variability associated with these methods are:

- **Within-individual day-to-day variability:** Perhaps the single most important source of error in the assessment of dietary intake, the methods for evaluating the true impact of within-individual variability, is the continued focus of much of the effort in this field. (Beaton et al., 1979; Guenther et al., 1997; Nelson et al., 1989; Sempos et al., 1985; Tarasuk & Beaton, 1992; Wu et al., 1986) provide useful discussions of this issue.
- **Gender:** Beaton et al. (1979) and Wu et al. (1986) are just two examples of the importance of this variable.
- **Temporal issues:** The day of the week (weekday versus weekend), number of days collected, consecutive versus random sampling, and time of the year are examples of temporal factors that can influence the reliability of dietary records as accurate reflections of “usual intake” (Basiotis et al., 1987; Post et al., 1987; Tarasuk & Beaton, 1992).
Measurement error: The inherent bias in the measurement of dietary intake may be the result of several possible sources of errors both inherent to the tool used and to the subjects being evaluated, e.g., reporting errors. Because measurement error can have a potentially significant impact on the interpretation of a given data set, many investigators have suggested that it should be accounted for in both the design and analyses of dietary intake data: (Anderson, 1986; Carroll et al., 1998; El Lozy, 1983; Kipnis et al., 1997; Livingstone, 1995).

Accuracy of nutrient databases: Advances in methodology over time will result in changes in the data on the nutrient composition of foods, a critical issue in establishing temporal nutrient/disease relationships (Anderson, 1986).

Factors that affect memory: As most of the data in the areas of dietary tracking and diet/disease relationships are collected via the use of recall methods, e.g., food frequency questionnaires or diet-recall, such factors as intelligence, age, mood, attention, frequency, and clarity of instruction will be important influences (Krall et al., 1988).

Although all these factors are always of concern, many are even more important in the assessment of dietary habits of infants and children (Persson & Carlgren, 1984; Post et al., 1987; Quandt, 1987).

Based on the deliberations of a distinguished panel of experts in the field of nutritional epidemiology, Anderson (1986) proposed several principles to be considered in the design of studies to assess temporal patterns of dietary intake:

- Sampling procedures should be equivalent across all time points studied.
- Methods should be equivalent across all time points.
- Because values in food composition tables may change over time, food composition databases used should accurately reflect the actual composition of foods available at each time point.
- Trends observed over a short time frame should be interpreted cautiously and not generalized until confirmed for a longer time span. Differences smaller than methodologic error may not be detectable, particularly if a time trend is based on only two time periods.
- Despite certain limitations (outlined in Riten, 1998) and depending on the question(s) asked, per capita food availability may be useful for estimation of time trends in consumption of specific foods or food components.

Anderson (1986) also offered several suggestions specific to studies of diet/disease relationships:

- Independent, dependent, and associated or confounding variables must all be clearly defined,
- Estimates of relationships tend to reflect the corresponding target population values even when probability sampling is not used. However, probability sampling provides a mathematical basis for generalization.
- The statistical considerations pertaining to comparison of groups and analysis of relationships also apply to intervention trials and clinical studies.

B. STUDIES OF DIETARY TRACKING IN CHILDREN

Despite the methodological issues discussed above and other limitations pointed out in Table 1, the studies abstracted indicate a consistent pattern of nutrient tracking that may begin as early as three years of age. As seen in Table 1, a number of studies have been designed to address the specific question of tracking of dietary
intake with varying results. A significant limitation of these studies is the small number of diet records collected from the subjects, often either single 24 hour recall or food frequency questionnaires. Nelson et al. (1989) suggested that upwards of 28 days of diet records need to be collected in order to control for intra- and inter-individual variation in intakes of specific nutrients.
Table 1: Tracking of Nutrient Intakes: From Child to Adult

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Subject Number and Description</th>
<th>Methods Outcome Variables</th>
<th>Results and Authors’ Conclusions</th>
<th>Comments</th>
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<tr>
<td>Amsterdam Growth and Health Study (Twisk et al., 1997; Welten et al., 1997)</td>
<td>182 subjects (98 ♀, 84 ♂) aged 13 at the start of the study.</td>
<td>Dietary measurements were collected a total of 6 times over 15-year period; annually over the first four years (ages 13-17), once each at ages 21 and 27. A food frequency/dietary history interview was used with a one month reference period. Parent/caregivers were questioned about qualitative details, e.g., skim vs whole milk etc. Welten et al. focused on calcium and dairy intake; macronutrient intake was a focus of the Twisk et al. (1997) report.</td>
<td>Based on their tracking analysis Welten et al. (1997) concluded that &quot;...the predictability of adolescent measurements of calcium and dairy food intake for measurements at adult age is only moderate in males and even lower in females.&quot; &quot;...based on the percentages of subjects continuously in the same quartile of calcium and dairy intake over a period of 12 years, in general the predictability of calcium and dairy intake was also moderate in both sexes.&quot; Twisk et al. (1997) concluded that the tracking of &quot;...the dietary parameters [protein, fat, and carbohydrates] over a 15-year period was quite low.&quot; Particularly compared to the tracking of serum cholesterol.</td>
<td>The use of only 6 retrospective measures of intake over a period of 15 years might have limited the validity of these data sets.</td>
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<tr>
<td>Study (Reference)</td>
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| Bogalusa Heart Study Nicklas, 1995; Nicklas et al., 1993; 1995 | The Bogalusa Heart Study involved collection of dietary data from 6 cohorts of 10-year-olds (n=1,439) and 2 cohorts of 13-year-olds (n=360) from a biracial (black and white) community. Additional cohorts of infants 6 months to 4 years and again at 10 years were collected, as well as a cohort of 10 to 17 year-olds who were assessed biannually. | These cross-sectional studies were designed to determine secular trends in dietary intake specific age groups, i.e., 10- and 13-year-old children. Comparisons were made between same age cohorts interviewed at different time periods (1976, 1978, 1981, 1984, and 1987 for the 10-yr-olds and 1976 and 1987 for the 13-yr-olds). A single 24-hour dietary recall was collected from each subject using a structured face-to-face interview. The procedure was adapted for caregivers of infants in the younger cohort. A single food composition database (periodically updated) was used to assess all dietary data. | Dietary intake:  
- total energy increased in all age groups and was greater than the 1989 RDA.  
- sucrose was about 18%, of total calories,  
- a low polyunsaturated:saturated fat ratio was reported, suggesting a relatively high intake of saturated fat.  
- sodium intakes at all ages were higher than reported levels in adults (mean 3.33g)  
- "in general, the composition of the diet remains similar at various ages when expressed per thousand calories."  
Trends: based on the data from 10-yr-olds  
- total energy: Nicklas (1995) stated that total energy "remained virtually the same..." Although data table presented a statistically significant (p<0.01) negative trend in total calories over the study period. No difference by race but boys consumed more than girls  
- other statistically significant negative trends were reported for total, saturated, and monounsaturated fat.  
- positive trends were reported for protein, carbohydrate, cholesterol, and sodium. | Because the cohorts were studied independently, it was not possible to assess within-individual tracking of dietary intake patterns. |
<table>
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<th>Study (Reference)</th>
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<th>Results and Authors' Conclusions</th>
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<td>Class of 1989 Study (Kelder et al., 1994)</td>
<td>At baseline 2376 subjects participated in an annual behavioral assessment starting in 6th grade and continuing through to 12th grade.</td>
<td>The measure used was a self-reported food preference questionnaire designed to assess dietary intake. Subjects were asked to select from 18 food pairs the “one food they would usually eat when they had the choice.” The food choice score was divided into quintiles. Tracking was assessed by dividing baseline values into quintiles and computing the subsequent mean values for students originally in those categories. “If a mean value within any sixth grade category maintained a relative position in rank compared with that in the other categories, this was interpreted as evidence of tracking.”</td>
<td>Tracking of both physical activity and food choice variables was apparent. Tracking was particularly evident in the reference group a evidenced by a non-significant test for differential trend. “In nearly all the follow-up periods, the students identified at baseline as measuring high remained high, and those measuring low remained low.” Authors concluded that “there is evidence of early consolidation and tracking of physical activity and food preference.” &quot;The early consolidation of health behaviors implies that interventions should begin prior to sixth grade, before behavioral patterns are resistant to change.”</td>
<td>Minimal details provided about the diet study.</td>
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<td>Framingham Children's Study (Singer et al., 1995)</td>
<td>105 two-parent families (third- or fourth-generation offspring of Framingham Heart Study participants) with a biological child (aged 3-5) were enlisted. This study reports results of analysis of diet records from 95 children (37 girls and 58 boys).</td>
<td>Diet was assessed each year using 3-day diet diaries. In the first year, 4 sets of diaries (one for each season) were collected, in years 2, 3, and 5 two sets, and one set in years 4 and 6. Diets were evaluated for total energy and 10 specific nutrients (protein, carbohydrate, total fat, saturated fat, mon- and polyunsaturated fats, cholesterol, calcium, potassium, and sodium). Diet records were averaged for each of three age groups: 3 to 4 (n=77), 5 to 6 (n=86), and 7 to 8 (n=91). Intakes were classified by quintiles and consistency was compared across the three age groups to establish tracking patterns.</td>
<td>Intakes of all nutrients except cholesterol increased with age. Total energy intakes were at or below the 1989 RDA at all three age periods. Protein intakes were above the RDA. Total fat as a % of calories was about 33% at all three age periods. Total protein intake was greater than the RDA; as a % of calories was consistently around 14% at all three periods. Carbohydrate as a % of calories was also consistent at about 55%. Consistency of classification was strong: 35.7% to 57.1% of children in the highest quintile of intake at age 3-4 remained in the quintile at age 5-6 and 57% to 86% remained in the top two quintiles. At age 7-8 40% to 67% of those with the highest intake at baseline were still in the top quintile and 60 to 93% remained in the top two quintiles. Results were the same in the lowest quintiles.” Three nutrients with poorest tracking were sodium, cholesterol, and polyunsaturated fat.</td>
<td>No reference group included. All subjects were from families in the Framingham study. Limits the generalizability of nutrient intake data, but not necessarily the validity of the tracking phenomena. The authors acknowledged the use of two different nutrient databases for analysis of diet records. Internal correlation studies found good agreement between the two systems. Tested for impact of compliance. Analyzed data from 64 subjects who participated at all three time periods and found that “the correlation coefficients were essentially unchanged from those presented.&quot;</td>
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<td>Paris, France (Deheeger et al., 1996)</td>
<td>278 children were enrolled at 10 months of age and subsequently evaluated at 2, 4, 6, and 8 years. 112 subjects remained until 8 years.</td>
<td>Diet histories, including a 24-hour recall, were collected on the subjects' birthday by interview with mothers. Nutrients analyzed included total energy, protein, fat, and carbohydrate. Anthropometric data (weight and height) were also collected. Correlational analyses were performed between nutrient intakes at all age periods and at 8 years. Body mass index (BMI) was also correlated in a similar fashion.</td>
<td>BMI at all ages beginning at 10 months was highly correlated with BMI at 8 years. However, less than 50% of the subjects remained in the same tertile category of BMI at 10 months and 8 years. As a % of total calories protein was stable, fat increased, and carbohydrates decreased over time. Only energy and protein intakes at 10 months were correlated with intakes at 8 years. By 2 years all nutrients studied except carbohydrate were significantly correlated with intakes at 8 years. At 4 years intakes of all nutrients were significantly correlated with intakes at 8 years.</td>
<td>Although both diet history (modified food frequency interview) and 24-hour recalls were collected, the data sets were limited to one/year. Correlational analysis between BMI and nutrient intake was not performed.</td>
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CHAPTER 3. CASE-STUDY: OBESITY AS A RISK FACTOR/BIOMARKER FOR MULTIPLE DISEASES OF ADULTHOOD

A. INTRODUCTION

Overweight in childhood and adolescence has become an important public health issue, because of concerns that overweight children and adolescents become overweight adults and overweight adults are at increased risk for adverse health outcomes (Troiano et al., 1995). The role of excessive body weight and body fat in increased mortality and morbidity from CVD, some forms of cancer, diabetes, and digestive diseases has driven much of the national diet and health care agenda (National Research Council [NRC], 1989; U.S. Department of Health and Human Services, 1988).

Among the questions focusing the debate about the long-term implications of obesity in children are:

- Do obese children become obese adults? Conversely, were obese adults obese as children?
- Does prevention of obesity during childhood prevent obesity in adults?
- Is obesity a condition caused solely by environmental factors, i.e., excess caloric intake and inactivity?
- What is the interaction between environment and genetic endowment? (Bouchard, 1995)
- Are normal weight adults at risk for chronic disease as a consequence of obesity during their childhood, i.e., is childhood obesity an independent risk factor for adult disease?

B. MEASUREMENT ISSUES

A lack of consensus exists with regard to the classification of children and adolescents as overweight or obese (Flegal, 1993; Obarzanek, 1993). Power et al. (1997b) points out that the actual classification of obesity requires not only a relevant cut-off but an accurate, reproducible measure of body fat. With regard to measurement, anthropometric measures, e.g., weight and height, are most often used in population studies for the generation of a body mass index (BMI; weight/height²). Actual adiposity distribution is commonly measured by comparing fat thickness at various body sites such as the triceps, biceps, subscapular. Power et al. (1997b) cautioned that special consideration should be given to adjustment for age and maturational development in the evaluation of obesity in children.

With regard to cut-offs used to classify obesity in children and adolescents, recent estimates of overweight prevalence for children and adolescents have used the 85th and 95th percentile of BMI as the basis for such estimates. The 95th percentile of BMI presumably represents overweight and is likely to have a high specificity for excess body fat. It has been proposed that a BMI at or above the 85th percentile but less than the 95th percentile be used to identify children and adolescents who are overweight and those who are above the 95th be classified as obese (Himes & Dietz, 1994). Power et al. (1997b) suggested that the choice of a cut-off “…defines both the prevalence of obesity and also the strength of its association with later outcomes.”

An additional practical concern about characterizing children or adolescents as overweight or obese is that such a label can lead to undue attention to body size and thereby increase the potential for eating disorders (DeJong, 1980; Maloney et al., 1989). Because of this potential adverse outcome, Troiano (1995) proposed that the 95th percentile cutoff be used as a criterion of overweight for children and adolescents rather than the 85th percentile. Children and adolescents with a BMI above the 95th percentile are most likely to be obese and at risk for
continued weight problems and adverse health outcomes in adulthood. Troiano et al. (1995) further commented that, because the association between risk of adverse health outcomes in adult life is much greater in obese adolescents than obese younger children, additional care must be taken when they are classified as overweight.

C. EPIDEMIOLOGY

The most recent estimates of the prevalence of overweight among U.S. children and adolescents are from the third National Health and Nutrition Examination Survey (NHANES III 1988-94). Phase 1 was conducted from 1988 to 1991 and Phase 2 was conducted between 1991 and 1994. Trend data on overweight prevalence are available from the second and third National Health Examination Surveys (NHES II 1963-65 and NHES III 1966-70), NHANES I (1971-74), NHANES II (1976-80), and NHANES III, Phase I (1988-91). The 85th and 95th percentiles of BMI used for defining obesity were estimated from National Health Examination Survey (NHES) II (for children 6-11 y) and III (for children 12-17 y).

1. Children 5-12 years old

Based on analysis of the data from NHANES III 1988-94, approximately 14% of children between 6 and 11 years of age were overweight, using the 95th percentile BMI cutoff points (see LSRO, 1999, Table IV-4). Prevalence rates were higher among Mexican-American and non-Hispanic black children than among non-Hispanic white children. Based on an analysis of NHANES III Phase 1 data, between 1988 and 1991 overweight prevalence for children 6-11 years of age was 11% using the 95th percentile BMI cutoff and 22% based using the 85th percentile of BMI (see LSRO, 1999; Table IV-5).

Comparisons of NHANES III Phase 1 data with earlier surveys have indicated that overweight prevalence (based on 85th and 95th percentiles for BMI) among children aged 6-11 years has increased, with the largest increases occurring since NHANES II (see LSRO, 1999; Table IV-6). Overall, increases in overweight prevalence between NHANES II and NHANES III, Phase 1 were greater for black children than for white children. Findings from the entire NHANES III 1988-1994 indicated generally higher overweight prevalence rates than those from NHANES III, Phase 1 alone (see LSRO, 1999; Tables IV-4 and IV-5), suggesting that the prevalence of overweight among American children has continued to increase. Weight increases occurred in both sexes across all racial and ethnic groups.

2. Adolescents 12-20 years old

According to the most recent estimates from NHANES III 1988-94, almost 12% of adolescents 12-17 years of age were overweight using the 95th percentile BMI cutoff points (see LSRO, 1999; Table IV-4). Overweight prevalence was similar among males and females, with higher prevalence rates found among Non-Hispanic black and Mexican American adolescents than non-Hispanic white adolescents. In an analysis of NHANES III 1998-91 data using the 95th percentile BMI cutoff, 11% of adolescents 12-17 years of age were overweight across race and ethnic groups (see LSRO, 1999; Table IV-5). When overweight was estimated with the 85th percentile of BMI, the prevalence of overweight was 22%. Mexican American males had a higher overweight prevalence than non-Hispanic white and black males. Non-Hispanic black females had a higher prevalence of overweight than Mexican-American and non-Hispanic white females.
As suggested by the evidence above, the prevalence of overweight among U.S. adolescents is continuing to increase. The complete NHANES III 1988-94 dataset indicates generally higher overweight prevalence rates than those found in NHANES III, Phase 1. Increases in overweight prevalence were apparent among males and females across all racial/ethnic groups.

Troiano et al. (1995) found that U.S. adolescents have become increasingly overweight since the mid 1960s, with the greatest increases occurring between NHANES II 1976-80 and NHANES III 1988-91 (see Table IV-6). During this time, age-adjusted prevalence rates were higher for black adolescents than for white adolescents using the 85th and 95th percentile cutoffs. With the 95th percentile cutoff, the increase in overweight prevalence was highest among white males (from 5% to 14%) across sex/race groups, and with the 85th percentile cutoff, it was highest among black females (from 18% to 30%).

3. **Do obese children become obese adults? Tracking**

Upon review of the most recent studies of the relationship between obesity in childhood and subsequent obesity in adults, the answer is an equivocal yes. Aside from methodological inconsistencies, e.g., standards for defining obesity and measures used to determine body composition, the equivocation derives from the fact that the association between childhood and adulthood obesity becomes stronger as the children grow older. From the limited data available on young children, it appears that risk for obesity as an adult is relatively small particularly in overweight children whose parents are not obese. However, the risk rises as the child grows older, so that those obese children older than ten are at increased risk of becoming obese adults, and that risk is magnified if at least one of the child’s parents are obese.

Serdula et al. (1993) reviewed the relationship between obesity in childhood and adult obesity on the basis of studies reported between the period of 1970 and 1992. In their summary, they observed that despite the wide range of data consequent to methodological inconsistencies between studies, there was a consistency between anthropometric measures in childhood and adulthood. Serdula et al. (1993) concluded that risk for adult obesity increased with age of childhood obesity and was even higher for very obese children. Based on the review of the studies listed in Table 3, it is apparent that these conclusion not only hold true but have been reinforced by recent studies of these relationships.

D. **DIETARY AND ENVIRONMENTAL LINKS TO OBESITY: ENERGY BALANCE AND INCREASED OVERWEIGHT PREVALENCE**

1. **Dietary factors**

It has been suggested that the increasing prevalence of excess weight and body fat among U.S. children and adolescents reflects a population shift toward positive energy balance in which energy intake exceeds energy expenditure (National Center for Chronic Disease Prevention and Health, 1997; Troiano et al., 1995). Troiano et al. (1995) suggested that the increase in the prevalence of overweight among children and adolescents may be more a result of a decrease in physical activity than an increase in energy input.

Nevertheless, current dietary and activity patterns of children and adolescents are believed to contribute to excess weight gain (Christoffel & Ariza, 1998; Troiano et al., 1995; Troiano & Flegal, 1998). Consumption of fast foods and other away-from-home foods by children and adolescents is frequent and more popular than ever before (LSRO, 1999). Away-from-home eating is associated with higher energy, fat, and saturated-fat
intake than at-home eating (Lin & Guthrie, 1996). Concurrently, contemporary children and adolescents may be more sedentary than those of previous years, leading to increased prevalence of excessive positive energy balances (LSRO, 1999). Overweight in adolescence has been associated with a higher risk of overweight in adulthood and may increase the risk of adverse health outcomes later in life (DiPietro et al., 1994; Guo et al., 1994; Serdula et al., 1993). Guo et al. (1994) reported that the risk that an overweight child will remain overweight as an adult increases with age. The predictive value for overweight during adulthood is excellent for an 18-year-old who is overweight and is good for an overweight 13-year-old.

2. Activity

Physical activity has been demonstrated to be inversely associated with risk for cardiovascular disease (CVD) in adults (Lee et al., 1999; Mensink et al., 1996). Efforts have been made to link physical activity in children to reduced risk factors for CVD, e.g., reduced total and visceral body fat (Owens et al., 1999) and blood lipid profiles (Suter & Hawes, 1993).

A concomitant of reduced activity level that has received some attention is the amount of time watching television (Robinson, 1998). Based on the analysis of data from NHANES III 1988-94, children aged 8-16 years who watched >4 hours of television each day had significantly greater body fat and a greater BMI than those who watched <2 hours per day (Andersen et al., 1998). A similar relationship was reported by Ross & Pate (1987) from a national sample of 6-9-year-old children. Dietz & Gortmaker (1985) found that overweight prevalence increased 2% for each additional hour of television watched per day in adolescents aged 12-17 years. Tucker (1986), on the other hand, found no relationship between television viewing and BMI in a cross-sectional study of high school male adolescents. Robinson (1998) reported only a weak, if any, association between television viewing time and adiposity among females in the sixth and seventh grades.

Klesges et al. (1993) showed that television viewing may increase children’s risk for excessive weight by decreasing overall metabolic rates. After watching television for 25 minutes, resting metabolic rates were found to decline by 12% in girls aged 8-12 years of normal weight and 16% in obese girls of this age range.

3. Genetics or environment

Although considerable evidence exists attesting to the increased risk for obesity associated with having obese parents, the heritability of obesity and its concomitants, e.g., body type, fat distribution, metabolism, remain to be fully elucidated (Bouchard, 1995; Rees, 1993). Although genetics clearly is an important factor associated with obesity within families, not all obese children have obese parents, and not all parents of obese children are obese. Other environmental based predictors of adult obesity that have been studied include:

- Low socioeconomic status (SES) of a child’s parents and school failure in childhood. In a study by Pine et al. (1997) of 700 youths who were psychiatrically assessed at a mean age of 14 years and again at 22 years, obesity in early adulthood was associated with low SES, poor physical health, smoking, and alcohol use in adolescence. When these factors were controlled, a relationship was found between early adulthood obesity and adolescent conduct disorders characterized by recurrent, impulsive aggression (Pine et al., 1997).

- Various psychological variables are associated with adolescent obesity, including emotional disorders, psychopathologies, and troubled parent-child dynamics (Lissau & Sørensen, 1994; Pine et al., 1997).
* In families where food is abundant and physical activity is not encouraged, overweight can result without specific psychological or physiological origins (Rees, 1993).

E. DOES CHILDHOOD OBESITY INCREASE THE RISK FOR ADULT DISEASE?

Obesity is associated with increased rates of all-cause morbidity and mortality in adults (Solomon & Manson, 1997). Despite inconsistencies in methodology (e.g., use of different standards for defining obesity) and design (e.g., longitudinal versus case-control), the evidence supports the contention that the risk for all-cause morbidity and mortality in adults is greater for obese children, particularly post-pubescent children. Minimal risk has been associated with obesity in younger children or infants. Of the studies done to date, it appears that childhood obesity especially in older children is an independent risk factor for adult morbidity and mortality. However, it should be noted that many of the studies designed to address this question did not include data on adult adiposity. As summarized in Table 2, obesity in childhood has been linked to risk factors for numerous diseases of adulthood. With the exception of one study (Mossberg, 1989), no attempts have been made to include dietary factors in making the association between childhood obesity and adult disease. Consequently, the role of diet per se in this relationship is unclear.
Table 2: Childhood Obesity: Risk Factor for Adult Disease

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<td>Bogalusa Heart Study (Freedman et al., 1987)</td>
<td>1,490 subjects (41% Black; 52% 9') who participated in four cycles of the study and who had anthropometry performed were included in this analysis. The mean number of years of involvement was 8.4; initial ages ranged from 2 to 14 years (mean 7.3 years); age range at the last cycle was 10 to 24 years (mean 15.7 yrs).</td>
<td>At each of the four cycles, height, weight, weight/height indices (Rohrer and relative weight), triceps skinfold thickness (TSF), physical development (Tanner staging). Tracking of obesity measures (TSF and Rohrer) was accomplished by categorizing subjects as lean (&lt;15th percentile), 15 to 85th percentile, obese/overweight (&gt;85th percentile). Measured both the predictive value, i.e., the probability that a child initially identified as obese will remain so in subsequent evaluations, and the sensitivity, i.e., the probability that a subject identified at the end of the study as obese/overweight had been so at previous examinations.</td>
<td>Reported that “TSF and Rohrer index in children are moderately predictive of levels eight years later; r = 0.54 and 0.67, respectively.” “However, tracking of obesity/overweight differs according to race-sex group and age; correlation were weakest in white females and preschool children, and strongest in Black females. 43% of children classified as obese initially remained obese at the end of the study.”</td>
<td>Rohrer index was used rather than BMI because it is “...only weakly correlated with height in early life..., but is similarly associated” with both subscapular and triceps skinfold. The 85th percentile of the Rohrer index was about equal to 110 percent relative weight.</td>
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<td>Meta-analysis (Guo et al., 1994)</td>
<td>Data from a total of 555 White subjects (277’r, 278 9’) from three longitudinal studies: Gils, Guidance, Harvard, and Oakland were used in this analysis. Subjects were all born between 1929 and 1960. No other demographic details were included in this analysis.</td>
<td>Data for stature or recumbent length (for ages 1 to 3 yr), and weight at ages 1 to 18 and at 35 years were used in this analysis. BMI values were computed and converted to percentiles for age and sex by using data from the second National Health and Nutrition Examination Survey (NHANES II). The upper limits of BMI for adults selected were 28 for males and 26 for females based on associations previously established with mortality.</td>
<td>The ability to predict adult obesity increased with age. Prediction of overweight at 35 y is “excellent at age 18 y, good at 13 y, but only moderate at ages younger than 13 y.” “The sensitivity and specificity of the chosen cutoff point (60th percentile of NHANES II BMI) were excellent for predicting overweight at 35 y from BMI values at age 18 y.” The sensitivity and specificity were less at ages 3, 8, and 13 and less for females than males.</td>
<td>The authors acknowledged the limitations of this analysis in terms of inconsistencies in exclusion criteria across the surveys.</td>
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<td>British Birth Cohort Study (Lake et al., 1997; Power et al., 1997a,b)</td>
<td>The British Cohort Study involved all children born in Scotland, Wales, and England between March 3 and 9, 1958. Data was collected from a total of 17,378 subjects (98% of target population). In addition to the indigenous cohort, immigrants were included at three of the sampling cycles. A total of 11,407 subjects (69% of the target pop) completed the full cycle. Data for 5700 9 and 5512 10 were analyzed. No other demographic details were provided in this report.</td>
<td>Data were collected at 7, 11, 16, 23, and 33 years. Data from immigrants were collected at 7, 11, and 16 years. Height and weight from primary subjects were measured at 7, 11, and 16 and 33 years and collected by self-report at age 23. The report by Lake et al. (1997), included height and weight from parents self reported when children were 11. BMI was calculated once for parents and at all time points for the children. Obesity was defined by the 85th percentile of the U.S. data</td>
<td>Power et al. (1997b) reported that correlations between childhood weight and adult BMI increased with age, being weakest in the younger children. &quot;Although the fattest children had the highest risks of adult obesity, most obese adults had not been fat at earlier ages; only 17% and 18% of obese 33 y old men and women respectively had been fat at age 7 y.&quot; Power et al. (1997a) observed that &quot;It is evident that the fattest 2% of adolescents at age 11 and 16 y have a high risk of obesity in adulthood. Risks for children identified at age 7 y are weaker, but are also elevated with a relative risk above 3.0...&quot; Lake et al. (1997) reported &quot;At each age of follow up, the mean BMI of the children increased as the parental BMI increased. Higher risks of adult (33 y) obesity were evident among children with overweight or obese parents: the odds for sons and daughters with two obese parents (compared with those with both parents of normal BMI) were 8.4 and 6.8, respectively. The children of two obese parents also showed the strongest child to adult tracking of BMI as indicated by the correlation between ages 7 and 33 y (r=0.46 and 0.54 for sons and daughters, respectively).&quot;</td>
<td>Justification of the use of the 85th percentile cut-off was that it &quot;...ensured adequate sample sizes in the obese groups.&quot; Power et al. (1997b) emphasized that &quot;the magnitude of the risk for fatter children depends on: the cut-off used to define overweight/obesity; the age of initial assessment and length of period follow-up; and the measure of adiposity.&quot; Power et al. (1997b) further observed that &quot;...the risk of adult obesity reduces when lower cut-offs are used to define overweight: for example, using the 91st centile in the 1958 cohort at age 7 y gives a relative risk of 4.0 and 3.2 for males and females respectively.&quot;</td>
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<td>British MRC Survey of Health and Development (Braddon et al., 1986)</td>
<td>Also referred to as the 1946 British Birth Cohort, this sample represents children born in one week in March of 1946 in England, Scotland, and Wales. A stratified samples representing 5362 individuals; of these 3322 were successfully contacted at age 36 y; of these anthropometric data were collected from 3249. No other demographic details were provided in this report.</td>
<td>Height and weight were collected by school staff at 7, 11, and 14 y and self reported at 20 and 26 y. For children (7, 11, and 14 y) “an index of relative weight was used to express measures of weight for height...weight expressed as a percentage of a standard weight, calculated for specified height, age, and sex. Data from this study was used to generate the standard. For adults, BMI was used as the standard. For the relative weight index, the cut-off ranges were &lt;90 (underweight), 90-110 (normal weight), 110-130 (overweight), and &gt;130 (obese). 100 was the standard weight and “obesity was roughly 20% above the standard” BMI cut-offs were 20, 25 and 30 for &amp; and 19.4, 24.3, and 29.1 for v.</td>
<td>The prevalence of both overweight and obesity varied with age and sex. Childhood obesity peaked at age 11 in both males and females, dropped through age 20, then increased again by age 36 with a higher prevalence in women than men. Overweight showed a similar pattern except more males were overweight by age 36 than females. “Only 21% of obese 36 year olds had been obese at age 11 years, and even when associated social factors were taken into account the correctly predicted percentage was much lower than the prediction rate achieved using body mass data from age 26.” “....among men obese at age 36, 51.3% were overweight but only 10.3% had been obese at age 11; but, 91.7% were above the normal weight range by age 26. Of the women obese at age 36, only 24% were overweight and 29.8 were obese at age 11. By age 26, 83% were above normal weight.”</td>
<td>In a pilot study of the effect of self reporting, the authors reported that “…self-reported heights and weights might have led to an underestimation of the prevalence of overweight at 20 and 26 y.” Because of difference in relative amounts of body fat, different BMI cut-off values were used for males and females.</td>
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<td>Centre International de l'Enfance, Paris (Rolland-Cachera et al., 1989)</td>
<td>Data from 135 subjects were included in this analysis: subjects were enlisted at age 1 y and followed through to “young adulthood” defined as growth in height of less than 1 cm during the year preceding the last measurement. 37 subjects were followed for the entire duration of the study (until at least 17 y of age). 98 subjects (age 18-25 y) were not available for at least some part of the study but were reintegrated into the protocol. The mean age of 135 subjects at the end of the study was 21.2 y. No other demographic details were provided in this report.</td>
<td>Correlational analyses were performed between individual anthropometric measurements (BMI, TSF, biceps skinfold [BSF], subscapular skinfold [SSF], and suprailiac skinfold [SISF]) recorded every year between 1 and 16 and measures at adulthood.</td>
<td>BMI “showed the best correlation between childhood and adulthood values in both sexes.” BMI was significantly correlated at all ages with BMI in adults. Correlations for the various skinfolds were better in males than females but varied from site to site. In males trunk skinfold sites were better than arm sites with BSF having the weakest correlations. Adult trunk skinfold were predictable in adult males from childhood measures. The reverse was true for females with arm sites performing better than trunk sites.</td>
<td>The study contained a relatively small sample size particularly when one considers that less than one-third of the subjects completed the entire protocol.</td>
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<td>Fels Longitudinal Study (Guo et al., 1997)</td>
<td>This report described a subset of the larger Fels Study. Subjects were 130 Caucasian ♂ and 114 Caucasian ♀.</td>
<td>Beginning at age 8, subjects had annual body measurements (skeletal age, total body fat [TBF], percent body fat [%BF], and fat-free mass [FFM]) collected through age 23 y. Only data from subjects who had at least 6 serial assessments were included in this analysis. Body density was determined by underwater weighing. Data for each subject were divided into two year periods (mean were used when subjects had two measures within the two-year period). Tracking was defined as &quot;...the extent to which individuals remained in the same percentile channel over time. The percentile channel was defined as the upper tertile of the study sample for each age.&quot; &quot;Sensitivity refers to the percentage of participants who remained in the upper tertile groups from one age to another. Specificity refers to the percentage of participants who remained in the combined middle and lower tertile group from one age to another.&quot; Tracking was evaluated at 5 year intervals corresponding to transition between pre-pubertal, pubertal, and post-pubertal periods.</td>
<td>Authors presented 3 major conclusions: &quot;1) there are gender-associated differences in patterns of change for %BF and FFM but not for TBF; 2) TBF, %BF, and FFM increased with increased rates of maturation. (At the same age, rapidly maturing children have significantly larger amount of TBF, %BF and FFM than slow maturing children); 3) significant tracking in body composition for individuals persists from childhood to adulthood.&quot; With regard to tracking the proportion of individuals tracking in a given tertile decreased with the length of interval, e.g., tracking was highest between 8 and 13 years but lower in the period between 8 and 18 years. In general, tracking in the post-pubertal years, i.e., &gt;13 y was greater than between the pre-pubertal years and post-pubertal years, e.g., 8 to 18.</td>
<td>The focus of the report was on the pre-and post-pubertal changes in body composition. No data on regional distribution of adiposity were collected. The level of methodological sophistication was significantly higher in this study than other similar surveys.</td>
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<td>Study (Reference)</td>
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<td>Harvard Growth Studies (Casey et al., 1992)</td>
<td>Of 296 Caucasian infants initially recruited, 134 (67♂, 67♀) were serially followed through age 18. Of these, 126 had follow-up visits at age 30 y, 120 at age 40, and 91 were seen at age 50 y. No other demographic details were provided in this report.</td>
<td>Weight and height were measured every three months for the first year, every 6 months between ages 1 and 10 y, yearly to age 18 y, at age 30, 40, and 50 (only weight). BMI was calculated (at age 50, BMI was calculated using height at age 40 y). Data were divided into 4 periods: childhood (ages 5-7 y) early adolescence (the 2 y before the year of peak height velocity), the year of peak height velocity, and late adolescence (2 y after the year of peak height velocity). Multiple BMI within each period were averaged. Height velocity curves were used to determine the point of maximal growth velocity. Correlational analyses were performed between BMI at 50 y and all other periods. Tracking was also assessed using the Foulkes-Davis tracking index; values of 0 indicate no tracking all curves intersect, and 1 indicates tracking of curves. Values of &gt;0.5 indicate tracking in the population because two individuals chosen at random would be more likely than not to have curves that do not cross.</td>
<td>Correlations between BMI at 50 y and all other ages were statistically significant (p&lt;0.05) for males. In females BMI in childhood was not correlated with BMI at &gt;30 y. At 30 and 40 y BMI of females was significantly correlated with all other periods except childhood. By age 50 BMI was weakly (year of peak height, 18 y) or not (childhood, early or late adolescence) correlated with any periods except at ages 30 and 40 years. Beyond adolescence, tracking of BMI into adulthood was significant for both sexes. At age 18 y both sexes had a “&gt;60% possibility that the measurement curves from age 18-50 y did not cross.” The tracking of BMI from childhood to middle age was better for males than females. The authors concluded “the prediction of ponderosity in middle age from BMIs early in life is more reliable for males than for females.”</td>
<td>No discussion of inclusion criteria (only 134 of a potential 296 subjects were included in this analysis), or attrition was included in the report. Part of the justification for the reliance on BMI was the use of the year of peak growth velocity rather than chronological age as the use of the former increases the accuracy of BMI as a measure of body size for growing children and adolescents.</td>
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<td>Muscatine Coronary Risk Factor Project (Clarke &amp; Lauer, 1993)</td>
<td>Original study cohort consisted of about 12,000 school-aged children in grade K-12 representing about 70% of available subjects. A total of 2631 young adults participated in at least one of two follow-up studies. The target ages were on or about the 23rd, 28th, and 33rd birthdays. The three age groups had the following age ranges: 20-25 (n=1471; 774 females, 697 males), 26-30 (n=1497; 807 ′, 690 ′), and 31-35 (n=574; 301 ′, 273 ′). No other demographic details were provided in this report.</td>
<td>Measurements included height, weight, BMI, and TSF. To conduct correlational analyses, the distribution for all measures was described by quintiles.</td>
<td>Correlations for weight ranged from in and in ′.</td>
<td>No data were available to perform correlations between children in the youngest groups, &lt;13 y, and the oldest group &gt;30 y. The authors concluded that &quot;...the majority of obese children become obese adults.&quot; Although the distributions of weight were divided into quintiles for the purpose of performing correlations, no attempt was made to describe the number of overweight or obese subjects. The mean values for BMI for all age groups were well within the limits of normal by most published standards. (BMI range was 23.7 to 27.1) with small standard deviations (range 3.9 to 5.4). Moreover, tracking correlations for TSF were smaller than the other measures with a higher percentage dropping from the higher quintiles as children to lower quintiles as adults. Consequently, rather than obesity, these investigators reported on the tracking of body size from post-pubescence to young adulthood.</td>
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<td>Osaka, Japan (Kotani et al., 1997)</td>
<td>From a cross-sectional cohort of 13,186 &quot;obese&quot; (out of a total available population of 203,088 children) evaluated over the course of over 20 years (1974-1995), a sub-population of 151 (90 ′, 61 ′) were identified who had reached the age criteria (&gt;20 y) for classification as adults and were available for the follow-up. Mean ages at initial exam were 10.5 ′ and 10.3 for ′ and 26.5 ′ and 27.4 ′ for ′ at follow-up. No other demographic details or inclusion criteria were provided in this report.</td>
<td>&quot;The criterion for obesity was when the student's body weight exceeded 120% of the standard body weight (SBW) for Japanese children, and that for extremely obese was those whose BW exceeded 140% of the SBW.&quot; SBW was based on &quot;a weight for height and sex chart for Japanese children devised on the statistical basis from nationwide survey data.&quot; In addition to anthropometry, overnight fasted blood samples were collected for analyses of triglycerides, total cholesterol, plasma glucose, and liver enzymes, GOT and GPT.</td>
<td>Over the course of the cross-sectional study, &quot;frequency of obese children increased from 5% to more than 10% and that of extremely obese children increased from 1% to more than 2% during these 22 y.&quot; &quot;These increases were most prominent in the schoolboys aged 9-11 y.&quot; In adults (&gt;20 y), &quot;...32.2% of the initially obese boys (relative risk: 5.3) and 41% of the initially obese girls (relative risk: 6.7) remained obese.&quot;</td>
<td>The extent non-compliance to follow-up in this study raises questions about the validity of the data.</td>
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<td>Study (Reference)</td>
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<td>Puget Sound (Whitaker et al., 1997)</td>
<td>Subjects were 854 infants (out of a potential sample of 1,333) born at an HMO between 1965 and 1971 and their parents. Inclusion criteria were: &quot;at least one weight measurement at the age of 21 y or older, at least one height measurement at the age of 18 or older for men and 16 years or older for women, no chronic conditions that might affect stature or weight (e.g., cancer or inflammatory bowel disease), and birth at a gestational age of 36 weeks or more.&quot;</td>
<td>Height and weight measures were taken from HMO records. Average BMI was calculated between 21 and 29 years of age. &quot;Adult obesity was defined as an average BMI of ≥27.8 for ♂ and 27.3 for ♀. &quot; The cutoff point for childhood obesity was &quot;a BMI at or above the 85th percentile for age and sex,&quot; while those with a BMI &gt;95th percentile were classified as &quot;very obese.&quot; The 85th and 95th percentile for BMI from both NHANES I and II were combined and used for the standard. Six age periods were defined, 5 between the ages of 1 and 17 y and one for 21-29. Parental BMI was calculated at the same time as the child’s examination at the mid-point of each time interval through 17 y. Parental obesity was defined as ≥27.8 for ♂ and ≥27.3 for ♀.</td>
<td>16% of the young adults were obese. The best predictor of adult obesity was parental obesity. &quot;Among those who were obese during childhood, the chance of obesity in adulthood ranged from 8% for 1-2 y olds without obese parents to 79% for 10-14 y olds with at least one obese parent. After controlling for parental obesity, the odd ratio for obesity in adulthood increased with age of obesity during childhood (lowest risk for youngest obese children, highest for obese children &gt;15 y). &quot;Obese children under three years of age without obese parents are at low risk for obesity in adulthood, but among older children, obesity is an increasingly important predictor of adult obesity, regardless of whether the parents are obese. Parental obesity more than doubles the risk of adult obesity among both obese and non-obese children under 10 years of age.&quot;</td>
<td>Although analyses between both mother and father and child’s BMI were performed, the authors did not specify if the child’s BMI was matched with the same sex parent.</td>
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<td>Stockholm Children’s Hospital Study (Mossberg, 1989)</td>
<td>504 children (233 ♀, 271 ♂) aged 0-16 (mean age 9.6 y) who were admitted to hospital for obesity were followed up at 10-year intervals. The original cohort was divided into 4 groups: &quot;I) diffuse obesity with onset before age 2 y (n=27), II) diffuse obesity with onset after age 2 y (n=397), III) children with fat distribution as in dystrophia adiposogenitalis (n=46), IV) children with onset of obesity after certain or probable brain damage (n=34).&quot;</td>
<td>In addition to measurement of weight and height at baseline, questionnaire were collected at follow-up to provide data on health history “degree of overweight,” dietary habits, social situation, children. Genetic influence was assessed by rating parents, grandparents, and other family members for body size. Four categories were used: slim/ordinary, plump, obese, or weight &gt;100 kg. Points were assigned for each category; parents received twice as many points as grandparents. Total points were calculated and a family score computed. Only 412 subjects had complete family records and were included in the analysis.</td>
<td>“The degree of obesity in the family (parents and grandparents) and the degree of overweight in puberty were the most important factors for weight level in adulthood.” “Even when their food intake was in accordance with recommended levels, obese children had higher than normal weight as adults.” “Excessive overweight in puberty was associated with higher than expected morbidity and mortality in adult life.” “The prevalence of chronic diseases for the whole study population (64.3%) was significantly higher that a non-obese Swedish reference population (52.8%). No difference were found among groups I-III; however Group IV had a significantly higher adult weight, along with earlier onset of obesity and lower weight/height in parents.</td>
<td>Aside from being admitted to a hospital for obesity, no other inclusion or exclusion criteria were described for the original cohort. Details of the dietary recall method and analyses were not clear.</td>
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<td>Harvard Growth Study (Must et al., 1992; Must, 1996)</td>
<td>Subjects were part of the third Harvard Growth Study. A total of 508 &quot;lean&quot; or &quot;obese&quot; subjects were eligible for the analysis. Of the 504 eligible for the study, 181 (81 male, 100 female) were interviewed, 161 (93 male, 68 female) were deceased, 83 declined and 83 were lost to follow-up.</td>
<td>Obese subjects defined as those who had BMI &gt;75th percentile (based on BMI from NHANES I) for any two years between 13 and 18 years of age. &quot;Lean&quot; was defined as maintenance of a BMI between the 25th and 50th percentiles between 13 and 18 years. A structured interview was used to gather data about health history.</td>
<td>For 2, the relative risks of death from all causes and death from coronary heart disease were approximately two times higher in those who were obese in adolescence than those who were lean. No increases were found in 2. For coronary heart disease, atherosclerosis, colorectal cancer (in 2), gout (in 2) and arthritis (in 2), the addition of adult BMI &quot;only slightly attenuated the risk associated with overweight in adolescence.&quot; By contrast, for non-insulin dependent diabetes mellitus, all of the effect of weight in adolescence was accounted for by overweight in adulthood. After exclusion of subjects who were taking antihypertensive medications (35%), systolic and diastolic blood pressure was normal in both weight groups and not significantly different between them. &quot;Overweight in adolescence increased the risk of morbidity for several conditions in men, women or both, and it compromised functional capacity in women. The increased risk was independent of adult BMI for all morbidity and mortality outcomes except NIDDM.&quot;</td>
<td>The justification offered for the use of the 75th percentile cut-off was that it increased the numbers of subjects thereby allowing for the provision of &quot;adequate power.&quot; Further, &quot;this percentile corresponds to the upper bound of suggested weights for young adults.&quot; 84% of the overweight group had a BMI that was &quot;above the 85th percentile at least once during high school; 26% exceeded the 95th percentile at least once during the same period.&quot; No analysis by gender was reported. No separate analyses were performed to determine whether differences in morbidity or mortality existed between those in &gt;75th vs &gt;85th vs &gt;95th percentiles. The authors acknowledged the potential sources of bias in the protocol. &quot;Bias due to loss to follow-up or misclassification of overweight or outcome could have distorted our results. Although vital status was determined for 84% of the cohort and although the rates of refusal to participate were comparable in the two weight groups, the possibility of bias due to loss to follow-up cannot be entirely excluded.&quot;</td>
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<td>Israeli Inductees Study (Lusky et al., 1996)</td>
<td>Study data was drawn from records of 110,000 17-year-old Jewish σ military inductees (10% foreign born). Subjects were categorized ethnically in order to establish weight category based on ethnically based BMI distributions.</td>
<td>The study was designed to determine whether 17 y-old extremely obese had a higher prevalence of “functional problems” than those with normal weight and “to describe the medical conditions associated with underweight and overweight in this population.” Relative weight was based on BMI and subjects were classified into five categories according to their ethnic specific BMI distribution: - severe underweight BMI &lt; 5th percentile - mild underweight: BMI between 5th and 15th percentile - normal: BMI between 15th and 85th percentile - mild overweight: between 85th and 95th percentile - severe overweight &gt;95th percentile Health assessments were based on standard medical examination. Functional impairment was defined by limitations sufficient to prevent assignment to active combat duty.</td>
<td>The prevalence of functional impairment was normal&lt; mildly underweight&lt; mildly overweight&lt; severely underweight&lt; severely overweight. All classifications were significantly greater than normal weight group. Hypertension and joint conditions of the lower extremities were positively associated with BMI. Functional problems associated with underweight included bronchial and lung conditions particularly asthma, and emotional disorders</td>
<td>The study was not intended to provide insight into tracking or long-term ramifications of BMI. Because of the focus on “functional” morbidity no other potential risk factors were assessed, e.g., serum lipids.</td>
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<td>Hagerstown, MD (Nieto et al., 1992)</td>
<td>The original cohort was 13,713 children who were 5-18 years old between the period 1933-1945.</td>
<td>This was a matched (sex, year of birth, and number of measurements during childhood) case (death)-control study designed to assess the relationship between childhood weight and growth rate and mortality. Children were categorized as either pre- or post-pubescent and ranked according to growth parameters (height z-score, height velocity, and relative weight). Relative weight was “defined internally, using as standard the distribution of weight for children of the same height, sex, and age. After exclusion for missing data and “extreme or erroneous” data, final subject pool was 13,146 (6,529 σ, 6,617 φ).</td>
<td>“Odds ratios increased linearly with prepubertal relative weight for both sexes combined and with postpubertal relative weight in females.” Although not statistically significant, growth rates and attained height were inversely related with mortality.</td>
<td>No data on weight, BMI or cause of mortality was presented for the adult cases.</td>
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<td>Stockholm Children's Hospital Study</td>
<td>504 children (233♂, 271♀) aged 0-16 (mean age 9.6 y) who were admitted to hospital between 1921-1947 for obesity were followed up at 10-year intervals (see Mossberg, 1989)</td>
<td>This study was intended to “supplement” earlier reports on this cohort (see Mossberg, 1989) with results based on “a more generalizable measure of overweight-the BMI.” Mean BMI was calculated for 9 time periods: 0-2 y, prepuberty (2-9 y for ♂, 2-7 y for ♀), puberty (9-15 for ♂, 7-13 for ♀), postpuberty (15-20 for ♂, 13-20 for ♀), and the midpoints of ages 20-29, 30-39, 40-49, 50-59, and 60-69. Follow-up data were collected on prevalence of CVD, diabetes, cancer (all types) and all-cause mortality.</td>
<td>See Mossberg, 1989 The 504 subjects seen for overweight as children were overweight as adults. ♀ were heavier than ♂ from postpuberty onward. “Our data suggest a lack of association between overweight in early childhood (i.e., pubertal stage) and adult morbidity and mortality.” “In contrast, however, the data show that subject who had died by the 40 year follow-up were heavier through adulthood compared to those still alive.” “…subjects who reported CVD during the 40 years of follow-up were significantly heavier at puberty and throughout adulthood compared to persons who did not report such disease.” “…subjects reporting diabetes experienced a marked increase in BMI between postpuberty and age 25 years and they remained significantly overweight in adulthood compared to those not reporting diabetes.” “…subjects reporting cancer had a lower BMI than those without cancer.”</td>
<td>See Mossberg, 1989</td>
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<td>Boyd-Orr Cohort (Gunnell et al., 1998)</td>
<td>The original cohort was 1,352 families in England and Scotland surveyed between 1937 and 1939. Data for this report is from members 2 to 4 y. All traced survey members who were alive and living in Britain on 1/1/1948 were included in the mortality analysis which include deaths up to 7/31/1995. Complete data on childhood BMI, social circumstances and adult SES were available for 1,165 ♂, and 1,234 ♀.</td>
<td>BMI were calculated as were z-scores using the 1990 British reference values for BMI as an “external” standard. Subjects were categorized into four groups (&lt;25th percentile, 25-49th percentile, &gt;50th ≤ 75th, and &gt;75th percentile. The 25th-49th category was used as the “reference category.”</td>
<td>“All-cause and cardiovascular mortality were associated with higher childhood BMIs.” Overall mortality rate was higher in ♂ than in ♀. “Study members who as children were above the 75th centile for BMI by modern-day standards, had about twice the risk of ischemic heart disease (IHD) compared with those whose BMI was between the 25th and 49th centiles.” “Those that were underweight in childhood were at increased risk of all-cause mortality compared with those of average weight.” “…the significant linear relationship with IHD was only seen in older children…” (those &gt;8 y).</td>
<td>No diet data, no data on weights or BMI as adults or age of onset of CVD.</td>
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CHAPTER 4. CANCER

A. CHILDHOOD DIET AS AN INDEPENDENT RISK FACTOR FOR SITE-SPECIFIC CANCERS

The majority of studies intended to focus on this question have been case-control studies utilizing retrospective historical data of dietary intake. For example, Egan et al. (1998) described risk factors associated with breast cancer in women on the basis of a case-control study involving 6705 cases and 9341 controls. Aside from family history, which was found to be a strong independent risk factor, several environmental factors were isolated, including diet (an inverse relationship with intake of carotene-rich foods). However, it is not possible from this type of data to determine at what point an increase in these types of foods or the amounts of putative active substances, e.g. β-carotene and/or other carotenoids, might be beneficial.

In those studies that have attempted to test for potential diet and cancer links beginning in childhood, the use of retrospective data and the lack of control for other potential confounding variables in the analyses make interpretation of the results difficult. An example of such a difficulty is in the report by Davies et al. (1996). This study was designed to test a hypothesized relationship between testicular cancer and consumption of dairy foods. Although the authors attempted to account for various sources of bias, the data revealed a potentially significant lack of control for demographic variables such as education and related lifestyle factors. Moreover, the reliance on retrospective data collected from subjects and their mothers, together with inconsistent response rates, could lead to misinterpretation of these data.

Several groups of investigators have focused on the potential relationship between childhood/adolescent lifestyle, e.g., dietary habits and exercise, and the risk of site-specific cancers. The utility of such studies is enhanced by knowledge of specific biomarkers and/or risk factors that emerge during specific developmental periods. The best example is breast cancer which is associated with several diet sensitive risk factors including delayed age at menarche, low body weight during adolescence, and greater height. Several studies have been designed to assess the impact of diet on these risk factors (Table 4). For example, Persky et al. (1992) looked at diet (vegetarian versus non-vegetarian) and hormone levels in adolescent girls. Petridou et al. (1996) studied the relationship between dietary factors (total fat, categories of fat, total energy) and age of onset of menarche.

Some case-control studies have focused on the potential risk associated with certain diets without addressing specific biomarkers of breast cancer (Pryor et al., 1989; Potischman et al., 1998). Tretli & Gaard (1996) performed an “ecological study” of the relationship between lifestyle changes that were imposed on adolescent girls during World War II to make inferences about the relationship between these changes (including diet) and subsequent development of breast cancer.

In many of the studies intended to test hypothesized diet and disease relationships, methodological inconsistencies have resulted in confusing and conflicting results. For example, Pryor et al. (1989) reported a positive association between breast cancer and intake of high fiber foods, specifically fruits and vegetables. These investigators speculated that the effect was due to increased intakes of β-carotene. By contrast, Egan et al. (1998) reported the exact opposite effect, i.e., a significant inverse relationship between intake of carotene-rich foods and risk, in women who had a family history of breast cancer. Diet data in both studies were retrospective, referenced to two years prior to study in Egan et al. (1998) and to adolescence in the Pryor et al. (1989) report. In neither case were total consumption of individual nutrients actually assessed. In the former study, carotene intake was estimated based on “reported frequency of consuming servings of cooked
and raw carrots and cooked and raw spinach 2 years before the interview.” The relationship was even more tenuous in the Pryor et al. (1989) in which only intake of high fiber foods, subsequently divided into fruits and vegetables and starchy foods was measured.

The majority of studies of the diet/cancer relationship have focused on food groups and, specifically food groups that have been associated with adult disease, e.g., high fat foods. Consequently, no data are available on the intake of total energy or specific nutrients that could be used to evaluate either tracking or an independent association between childhood intake and site-specific cancer in adults. Moreover, because of the nature of the analyses, i.e., generation of associated risks, what data were collected on diet were not evaluated in such a way as to be able to make inferences about tracking of these intake patterns from childhood to adulthood.

Other cancer sites that have been investigated include the prostate (Andersson et al., 1995; Slattery et al., 1990), gastrointestinal tract cancers (Hansson et al., 1994; La Vecchia et al., 1995), and testicular cancer (Davies et al., 1996) (Table 4).

B. CHILDHOOD OBESITY AS AN INDEPENDENT RISK FACTOR

BMI has been identified as a risk factor for numerous site-specific cancers, in particular, colon cancer (Shike, 1996) and breast cancer (Stoll, 1998). As documented in Table 4, a number of studies have included BMI in an attempt to ascertain childhood antecedents of site-specific cancer, with varying results. Positive associations were reported between BMI in adolescence (but not in adults) and risk for gastric cancer (Hansson et al., 1994) and breast cancer (Pryor et al., 1989). Andersson et al. (1995) reported no association between either adolescent or adult BMI and prostate cancer. Petridou et al. (1996) reported that larger BMI significantly accelerated the occurrence of menarche, which would be associated with a decreased risk of breast cancer. However, Stoll (1998) suggested that the protective effect associated with obesity-related early onset of menarche is “temporary and small, compared to the risk of increased promotion of carcinogenesis when obesity continues after the teenage years.”

Ballard-Barbash (1994) has recently summarized the often conflicting data on the relationship between body size and breast cancer by observing that “the contrasting effects of body size on pre-menopausal breast cancer compared with postmenopausal breast cancer and the lack of a strong association between body mass and postmenopausal breast cancer in some cohort studies has led to a view that obesity has little influence on breast cancer risk....Recent research suggests that, compared to body mass indices, adult weight gain and increased central body fat may be more specific markers of the metabolic consequences of obesity and therefore may predict health outcomes more consistently... Data on lifelong weight changes and the location of fat depots may more precisely identify women with high risk patterns...” As reinforced by Brinton & Swanson (1992) and Ziegler (1997), in addition to focusing on distribution of body fat, future research will need to more directly assess the relationship between specific timing of weight gain, energy balance, activity levels, and known risk factors, e.g., steroid hormone levels, in order to more accurately predict when and in whom breast cancer risk is affected.

Because many investigators have reported positive associations between BMI and various site-specific cancers, it is logical to assume that energy intake would also be considered a potential risk factor. In the studies reviewed in Table 4 that attempted to address childhood precursors of adult cancer, only two, Persky et al. (1992) and Petridou et al. (1996), contained specific data on nutrient consumption. However, as distinguished
from the majority of studies reviewed, the intention of these two studies was to assess prospectively the impact of diet on specific risk factors for breast cancer, i.e., hormone concentrations and age at menarche. Neither tested the possibility of tracking of the relationships being tested or the diet/outcome relationship in adults.

C. SUMMARY AND CONCLUSIONS

Much of the knowledge of the relationship between diet and cancer in humans has been provided by population-based epidemiological studies. However, because of the lack of either specific traceable biomarkers and/or prospective data beginning in childhood, it is not possible to determine at what point this association might begin or when a prophylactic intervention might be appropriate. Furthermore, because none of the case-control population-based studies reviewed included analysis of individual nutrients it is only possible to make general inferences based on food groups about potential diet/cancer links. Finally, because of the nature of the analyses performed in studies done to date, it is not possible to determine whether the intakes of suspected foods or food groups track from diets of children to those of adults.

In addition to all the problems associated with case-control or population-based epidemiological studies, a specific issue in those studies that have addressed the BMI relationship has been the absence of attempts to corroborate retrospective recall anthropometric data by reference to medical records. Further, none of the studies reviewed included a working definition of obesity and most used the control sample rather than the general population as the reference standard. The assumption is that the sample is representative of the population.

Based on the extant data about the tracking of obesity, i.e., the later obesity occurs, the more likely it is to track and have health consequence (see Chapter 3), interventions would seem to be better focused at population-based efforts to stem the increase in post-adolescent obesity in both individuals and the general population.
### Table 4a: Diet and Cancer: Risk Factors in Children

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<tr>
<th>Study/Venue (Reference)</th>
<th>Subject Number and Description</th>
<th>Methods Outcome Variables</th>
<th>Results and Authors' Conclusions</th>
<th>Comments</th>
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<td>Sweden; prostate cancer (Andersson et al., 1995)</td>
<td>The study population consisted of all men under 80 born in Sweden and living in a specific county in Sweden between 1989 and 1992. Of 343 eligible cases of prostate cancer, 256 (74.6%, mean age 70 ± 6.1 y) were included in the study. Of the 329 invited age-matched controls, 252 (76.6%, mean age 69.8 ± 6.2 y) completed the interview.</td>
<td>This population-based case-control study was designed to assess the relationship between early exposure to risk factors and prostate cancer in adults. Data were collected in three ways: - self-administered food frequency questionnaire about recent diet and diet 20 years earlier. - a structured interview by a blinded interviewer. The interview had 2 parts; questions about childhood and adolescence and questions focusing on adult habits and personal history. - a 20-item food frequency questionnaire focusing on specific food groups (dairy products, high fat/cholesterol foods, and other foods. The emphasis was on total fat and cholesterol intake.</td>
<td>“The main finding in this population-based case-control study of early life risk exposures was the lack of association between adolescent diet and the risk of prostate cancer.” “There was no substantial association between adult height or BMI and prostate cancer, but exercise appeared negatively associated with risk.”</td>
<td>Retrospective histories, particularly over long time periods, are notoriously unreliable for collection of valid diet data. Neither individual nutrient status nor use of dietary supplements were evaluated. The limited focus of the food frequency questionnaire precluded the possibility of evaluating total diet, other dietary components or interactions between other components and lipids. Although dismissed as being an artifact of chance, the authors found a trend (p&lt;0.07) towards an inverse relationship between butter consumption and prostate cancer. Recent studies have identified conjugated linoleic acid (CLA) as a potential anticarcinogenic agent in dairy foods.</td>
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<td>Sweden: gastric cancer (Hansson et al., 1994)</td>
<td>Study participants were resided in either a high or low incidence area of Sweden. <strong>Cases:</strong> n=338 (74% of those eligible, mean age 67.7 y: 218♂) <strong>Controls:</strong> n=679 frequency matched by age, sex, but not be geographical location (77% of those identified as eligible, mean age 67 y)</td>
<td>This case-control study was designed to evaluate the impact of height, weight at age 20 and socio-demographic factors on risk of gastric cancer. All subjects underwent a face-to-face structured interview to obtain data on height, weight, BMI, SES occupational, medical and dietary history. The reference periods were adolescence (apparently used 20 y as the reference point for adolescence) and 20 years prior to the interview. The process for obtaining dietary data was not described in this paper.</td>
<td>“Gastric cancer was negatively associated with height. Risk was positively associated with weight at age 20 in both sexes. The highest BMI quartile was associated with an increased risk. This association between BMI and risk was confined to BMI at age 20, and disappeared for BMI 20 years prior to the interview.” “...an increase of 5 BMI units increased the risk by 62% at age 20 but only 6% 20 years prior to interview.” This effect was similar across genders. In addition, socioeconomic factors were associated with risk. Higher SES and years of education were inversely related to risk. Number of siblings was positively associated with risk. This report did not include any food or nutrient-specific analyses.</td>
<td>Although subjects were recruited from areas with different incidence rates no analyses were performed to test for geographical effects. 20 years of age was used as the adolescence reference point. No attempts were made to confirm retrospective estimates of anthropometric measures. Subjects’ BMI values were divided into quartiles based on the distribution of the controls. Obesity was referred to often in the discussion but never defined. Large discrepancies between ♂ and ♀ were noted in the numbers of missing values for weight. 17% of ♀ values for both cases and controls were missing compared with 6 and 5% of the ♂ cases and controls.</td>
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<td>East Anglia, U.K. (Davies et al., 1996)</td>
<td>Cases n=129; mean age 42.7 y, BMI 22.6 Cancer controls: n=211; mean age 43.4, BMI 22.2 Population control: n=184; mean age 44.4, BMI 22.2 All subjects were from the same area of Eastern England and matched for “social class.” Cancer controls were matched for year of diagnosis</td>
<td>A case-control study designed to test the hypothesis that milk and dairy products are risk factors for testicular cancer. Data sources collected via mail were: - subject questionnaire about current consumption - where possible, subjects’ mothers reports on consumption patterns as adolescents (17 y old). The focus was on milk, dairy products, and fruits and vegetables.</td>
<td>Response rates of the cases and cancer controls were similar (73 and 65%, respectively) compared with 57% of the pop. controls. Response rates of the mothers were similar in all groups. In contrast to either the cases or cancer controls, more mothers (n=125) of population controls responded than sons (n=105). “Cases consumed significantly more milk in adolescence than population controls, but this difference did not apply to other dairy products or fruit. The consumption of milk by cancer controls was intermediate between cases and pop. controls. Cancer controls with non-epithelial cancers had a milk consumption similar to cases whereas subjects with epithelial cancers had a consumption similar to population controls.”</td>
<td>There were more non-manual workers in the population control group than cases, indicating a potential difference in education and/or other relevant factors. Subjects’ current consumption patterns were used as a surrogate for adolescent consumption patterns. Analyses were limited to food groups and food items. Use of dietary supplements were not included. Evidence of demographic differences, i.e., more non-manual workers in pop. controls, more maternal responses in pop. controls, raise the possibility of influence of other factors, e.g., education, attitudes and beliefs, lifestyle, on these outcomes.</td>
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<td>Italy: stomach cancer (La Vecchia et al., 1995)</td>
<td><strong>Cases</strong>: n=723 (443♂, 280♀; median age 61 y; range 19-74 y) diagnosed not later than 1 y before interview. <strong>Controls</strong>: n= 2,024 (1,189♂, 835♀; mean age 55 y; range 19-74 y) admitted to the same hospitals as cases in Milan, Italy, for “acute, non-neoplastic and non-digestive tract diseases unrelated to long-term modifications of diet and requiring hospital admission.”</td>
<td>This case-control study was intended to address the potential relationship between social factors and gastric cancer. The number of siblings was used as an “indirect indicator of living and, possibly, dietary conditions in childhood and adolescence.” Subjects were administered a structured interview which included questions about sociodemographic factors (including # siblings), anthropometrics, a problem-oriented medical history, family history of gastric and colorectal cancer, and frequency of consumption of “selected indicator foods.”</td>
<td>Cases were older than controls and significantly less educated and of lower social class. Subsequent analyses were adjusted for these variables. After stratification no significant interactions were observed between sex, age, and education. “The association with number of siblings was stronger in subjects above the age of 60 than in those under 60.”</td>
<td>The authors justified the validity of family size as an indicator of “poor living conditions” by noting that “larger families were probably a stronger indicator of poor living conditions in the earliest part of the century than more recently.” If that is true then conceivably it is not just the number of people in the house but rather other factors that are causing the effect. In the absence of any data on other factors that were affected as a result of these poor living conditions, e.g., diet, how can one ascertain the relevance of family size to gastric cancer today..</td>
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<td>Chicago: Vegetarian Breast Cancer study (Persky et al., 1992)</td>
<td>Vegetarian (n=35: mean age 16.2 y; BMI 22.8) and non-vegetarian (n=40; mean age 16.7; BMI 22.2) girls were recruited from private boarding schools. The vegetarian group was from a Seven-Day Adventist school that served a lacto-ovo-vegetarian menu.</td>
<td>&quot;The purpose of the current study was to explore hormonal differences among teenage girls whose nutritional intakes indicate varying risk of breast cancer specifically girls who ingest vegetarian or non-vegetarian diets.” Upon enrollment in the study, subjects completed a detailed medical history, including questions about previous hormone ingestion, menstrual history, medication use, current intake of alcohol, cigarettes and recreational drugs. Subjects also completed a 7-day activity schedule and 3-day diet record. Nonfasting blood samples were collected between day 11 and 13 and days 21 and 23 of menstrual cycles</td>
<td>&quot;The racial composition of the two schools were significantly different, with the vegetarian school containing a greater percentage of Hispanics and a lower percentage of non-Hispanic whites that the non-vegetarian school.” Percentages of Afro- and Asian Americans were similar in both schools. Vegetarians had significantly higher levels of polyunsaturated fats, calcium, iron, thiamine, riboflavin, and fiber and lower levels of total fat and protein as % of calories, saturated fats (total and % total calories), sucrose, starch, and caffeine. The results of the current study suggest that adolescent vegetarian girls have significantly higher levels of dehydroepiandrosterone sulfate (DHS) than adolescent non-vegetarian girls.” Despite the significant differences between groups for numerous dietary factors, no association was reported between any nutrient and DHS, suggesting that “DHS may be sensitive to a characteristic of vegetarian status other than the nutrients measured…”</td>
<td>The dietary questioning did not include history of use of dietary supplements. The timing relative to the blood samples of the activity and diet records was not reported. Lower levels of DHS had previously been reported to be associated with increased risk for breast cancer. No data on family history or analysis using this factor were included. No analyses by individual food categories, e.g., meat versus soy, were performed This study represented a &quot;snapshot in time&quot; approach. Longitudinal, case-control population data on the factors addressed herein are essential to determine the relevance of these findings.</td>
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<td>Greece: age of menarche (breast cancer) (Petridou et al., 1996)</td>
<td>Data from 176 menstruating and 179 non-menstruating girls ranging in age from &lt;10 (n=8 all in the non-menstruating group) to 16 y (7 girls &gt;15 were included in the menstruating group. None of the non-menstruating group were older than 14 y). Subjects were recruited from primary and secondary schools in “middle to upper middle class areas,” of Athens, Greece.</td>
<td>Early age at menarche is associated with increased risk for breast cancer. Consequently, this study was designed to ascertain whether energy, energy-adjusted fat, and/or macronutrient intake, or anthropometric variables are associated with age at menarche. Each student was interviewed in person and questioned about demographics and socioeconomic variables, menstrual status and history (mothers were also asked about age of onset of menarche and paternal education). Students also responded to a 124-item food frequency questionnaire referenced over the previous year. Physical activity and inactivity were also assessed via a questionnaire.</td>
<td>Maternal age at menarche, height and BMI were all significantly associated with accelerated occurrence of menarche. “Various measures of moderate physical activity as well as increased total energy intake were associated with a delay in age at menarche.” “Energy-adjusted macronutrients were not associated with age at menarche.”</td>
<td>The reference period for the food frequency questionnaire was the previous year which seems like a long time to ask children. The authors gave one reference where this tool was used in an adolescent population. The tool might have been validated in a pilot study of children in this population. 124-item questionnaire would seem to be a lot for children this age. Although intake of polyunsaturated fat was significantly associated with delay of age menarche, the authors dismissed it the findings because, “this result is not compatible with any biologically meaningful hypothesis...” “...it may well represent a manifestation of the multiple comparison process.”</td>
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<td>NCI: Diet and Breast Cancer (Potischman et al., 1998)</td>
<td>Subjects were recruited from three geographic areas: Seattle/Puget Sound, Atlanta, GA, and central New Jersey. <strong>Cases:</strong> 1647 ≤ 45 y with newly diagnosed breast cancer. <strong>Controls:</strong> 1501 control subjects recruited over the same time period (5/1/90 to 12/31/92) who were frequency matched by geographical area and age. <strong>In order to “validate”adolescent diet, mothers of cases (n=640; 66% of living mothers) and controls (n=564; 62% of living mothers) were recruited. Because of a significant difference in maternal response rate by race, only data from white case (509) and control (n=477) mothers were used in the final analyses.</strong></td>
<td>A case-control study designed to assess the relationship between diet (particularly intake of fat and fruits and vegetables) and development of early onset breast cancer. In addition to the collection of anthropometric, demographic, and other relevant data (reproductive and medical history, physical activity, weight changes, and alcohol consumption), subjects responded to a 29-item food frequency questionnaire about diet during ages 12-13 y or grade 7-8. Subjects also completed a self administered food frequency questionnaire regarding recent diet. Living mothers also completed a food frequency questionnaire for their offspring. The focus of the diet records was on fat and fruit and vegetable.</td>
<td>“Risk estimates and 95% confidence intervals adjusted for age, race, and study site were similar...” No statistically significant associations were found between diet and breast cancer. “These data do not provide evidence for a strong influence of dietary intakes during adolescence on risk of early-onset breast cancer.”</td>
<td>The addition of maternal recall was intended to provide corroboration to case recall. No descriptions or analyses were presented to characterize the respective study groups, e.g., demographic, ethnic, anthropometrics (BMI) etc.. The potential impact of the use of dietary supplements was not presented in the analyses. No analyses for activity or anthropometrics (height, BMI) were included in this reports. Did not test for potential interactions between diet and family history.</td>
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<td>Adolescent Diet Study: Utah Breast Cancer (Pryor et al., 1989)</td>
<td>Subjects were recruited from the population of Caucasian females between the ages of 20 and 54 y old living in 4 urban counties of Utah. Cases: (n=172; 70% of possible 246 possible cases) diagnosed between 12/1/80 and 5/31/83 with &quot;histologically confirmed first primary breast cancer. Controls: (n=190, 80% of 239 potential controls) selected by random-digit dialing, controls were matched within 5 y age groups. Two controls selected for each case.</td>
<td>The study was intended to assess how intake of dietary fat and fiber and/or body size during adolescence might be related to incidence of breast cancer in Caucasian females in Utah. Multiple regression analyses controlling for age, age at menarche, education, and age of first pregnancy were performed. Separate analyses were performed by menopausal history (pre vs post) A modified food frequency questionnaire with an emphasis on fat and fiber was administered by telephone. Neither total calories nor individual nutrients were assessed. In addition to diet, age, marital status education, income, religion, age at menarche, age at first pregnancy, menopausal status, family history of breast cancer, height and weight at age 18 y and as adults were collected. Reference period for adolescence was 12 y.</td>
<td>&quot;An elevated risk for highest quartile versus lowest was associated with a larger BMI at age 12 in pre-menopausal women; a larger adult BMI lowered the odds ratio for highest versus lowest quartile in pre-menopausal women; BMI did not alter risk in post-menopausal women.&quot; &quot;...fat from milk, cheese and yogurt reduced the odds ratios in both pre-menopausal and post-menopausal women.&quot; High fiber intake (associated with fruit and vegetables) produced elevated odds ratios in all three upper quartiles compared to the lowest quartile in post-menopausal women; although fiber from grains was associated with decreased risk for both pre- and post-menopausal women. Differences between pre- and post-menopausal women supports a hypothesized difference in cancers occurring at these periods.</td>
<td>&quot;The possibility of biased estimates from low response rates (cases=60%, control=61%), potential recall bias, and some lack of precision in the dietary instrument should be considered.&quot; Activity level was not assessed. Retrospective anthropometric data were not confirmed by medical records. No assessment of dietary supplement use were included. The authors speculated that the increased risk associated with fiber (fruits and vegetables) could be explained by increased intakes of β-carotene. However, this suggestion should be tempered by the report of Egan et al. (1998), who analyzed factors associated with risk in women with family histories of breast cancer, and found that intake of foods high in β-carotene was inversely associated with risk. The authors suggested that the reduced risk associated with dairy foods was associated with increased intake of other...</td>
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<td>Norway, breast cancer</td>
<td>All women born in Norway between 1903-1953 and between 30 and 59 years during the observation period, 1956-1992 were included in this analysis. 20,111 ♀ with breast cancer were included in the study.</td>
<td>Using a population based age cohort model, this study was designed to test the hypothesis that changes in lifestyle consequent to World War II (WWII) decreased the risk of breast cancer in Norway. The study was accomplished using two mathematical models utilizing grouping by age and by birth.</td>
<td>“The incidence of breast cancer was lower than expected among women who experienced puberty during the war. The estimated configuration of the exposure variable showed an increase in exposure up to the start of WWII to twice the level in 2926, dropped by 13% during the war, and increased again after the war.”</td>
<td>No direct measures of lifestyle, diet, measures of food security, demographics etc., were included in this study. The exact type and nature of the lifestyle changes responsible for these results could only be inferred from other sources of data. In their discussion the authors implied that the results were due largely to dietary factors and cited studies that had previously documented reductions in total energy, meat and meat products, milk products. They also referred to documentation of increased consumption of fish and fish products, fresh vegetables, and dietary fiber (related to potatoes, bread, and oats)</td>
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<td>Utah; Prostate cancer (Slattery et al., 1990)</td>
<td>Cases: (n=385) divided into two age group 45-67 y, 68-74 y. Controls: (n=679) aged matched by 5 y intervals. No differences were found between groups for education, income or religious affiliation.</td>
<td>This population-based case-control study conducted in Utah was designed to evaluate the risk of prostate cancer associated with fat consumption during adolescence and adulthood. An additional goal was to assess changes in dietary patterns between adolescence and adulthood and compare those patterns with national survey data. Analysis included adjustment for age as well as stratification by age. In a mailed questionnaire, subjects were asked about adolescent (ages 12-18) diet with the use of a 23-item food frequency questionnaire. An additional in-person structured interview was conducted to ascertain demographic background, medical history and diet. Dietary patterns were established with a recall referenced to the three years prior to diagnosis for cases and the previous three years in controls.</td>
<td>Changes in diets from adolescence to adulthood “corresponded to national changes in food consumption practices.” These changes included decreased consumption of eggs, whole milk, butter, white bread, cereals, and candy and increased consumption of red meat, fish, low-fat milk, cheese, yogurt, ice cream, margarine, fruits and vegetables, and whole wheat bread as adults compared to adolescence. Men who consumed a diet high in saturated fat as adults were at increased risk for aggressive prostate cancer after controlling for adolescent intake. However, men who ate diet high in saturated fat as adolescents were not at increased risk after controlling for adult intake.</td>
<td>The emphasis of this study was on the validation of the methods used to assess dietary intake retrospectively (during adolescence). The validation came from a comparison with national trends. Presumably if the diet changed and the change was consistent with national trends then the hypothesis was confirmed. However, as acknowledged by the authors “men did report the same frequency of consumption of various food groups during adolescent and adult years. It is possible that some men either maintained a consistent dietary pattern or reported their adult diet for the adolescent years.”</td>
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CHAPTER 5. CARDIOVASCULAR DISEASE (CVD)

A. INTRODUCTION

In an succinct synopsis of our understanding of the precursors of CVD including atherosclerosis, McGill et al. (1998) listed those factors that have been identified as predictors of adult disease. These risk factors include: age, gender (males are at higher risk than females), family history, high concentrations of total serum cholesterol and low-density lipoprotein (LDL) cholesterol, low levels of high-density lipoprotein (HDL) levels, a high LDL-HDL ratio, smoking, hypertension, obesity, and diabetes. Many of these risk factors have been linked to characteristic dietary patterns in adults and consequently much attention has been paid to interventions aimed at changing these patterns. Few data have been available on the time course of CVD vis-à-vis the diet and risk factor relationship. Several longitudinal studies have been conducted that have included an exploration of the emergence of these risk factors and their relationship to the development of adult disease. The following sections will include presentations of those data that have been used to address the association between the appearance of risk factors in children and the development of CVD in adults.

B. DO ADULT RISK FACTORS/BIOMARKERS APPEAR IN CHILDREN?

1. Review of extant data

A number of prospective cross-sectional epidemiological studies have been designed to collect data on cardiovascular risk factors beginning in childhood (Table 5a).

The Bogalusa Heart Study was a longitudinal cross-sectional study designed to evaluate the relationship between lifestyle (including diet), environmental, and demographic factors, and predictors of CVD. The study involved collection of dietary and clinical data from 6 cohorts of 10 year olds (n=1,439) and 2 cohorts of 13 year-olds (n=360) from a bi-racial (black and white) community in Louisiana. Additional cohorts of infants 6 months to 4 years and again at 10 years were collected, as well as a cohort of 10 to 17 year-olds who were assessed biannually. As noted by Berenson et al. (1997), the examination of “a total pediatric population over time that has aged into young adults, has provided an opportunity to observe changes during phases of growth and maturation,” and to determine how those changes might bear on the “early natural history of cardiovascular diseases.”

Srinivasan et al. (1996) summarized their analyses data from the Bogalusa cohort pertaining to the importance of age and sexual maturation on serum lipid composition by observing that “sexual maturation sees the establishment of adult lipoprotein patterns, especially in white individuals: higher levels of triglycerides, VLDL and LDL cholesterol and lower levels of HDL cholesterol in men than in women.”

Among the specific findings relative to serum lipid levels in children participating in the Bogalusa study are the following observations:

- Serum cholesterol concentrations decline in all children irrespective of age, sex, or race.
- High-density lipoprotein cholesterol (HDL): HDL concentrations tend to decline in both races and sexes, but to a greater extent in white males.
The maturity related decline in HDL is "even more pronounced" in white men with truncal obesity and hyperinsulinemia.

Low-density lipoproteins (LDL): concentrations decline slightly during puberty but begin to rise in both sexes and races.

Serum triglycerides and very-low density lipoprotein (VLDL) rise in all children during puberty, but the rise continues in post-pubescent white males.

The positive association between obesity and lipoproteins is strongest in white males and weakest in black females.

With regard to the relationship between race and serum lipids, Srinivasan & Berenson (1995) noted that

- racial differences are "clearly established by 9 years of age."
- black children have lower levels of triglycerides and VLDL-cholesterol and higher levels of total cholesterol. HDL-cholesterol and specific lipoprotein fragments (Apo A-1, apoE, and Lp[a]) than white children.

None of the analyses summarized by Srinivasan & Berenson (1995) included consideration of the contribution of diet.

Wattigney et al. (1995) evaluated data from young adults (n=1,928; ages 19-32) examined in the 1988-1991 Bogalusa survey to identify those at risk for CVD due to obesity, blood pressure, or serum lipid concentrations. In a subset of the larger cohort (n=1,587), data from previous evaluations as children (in the 1973-1974 survey) were available to assess tracking of risk factors from childhood through to young adulthood. Clustering or grouping of risk factors in young adults was also evaluated. Wattigney et al. (1995) reported that the occurrence of clinically significant levels of risk factors for CVD varied according to race and sex. More specifically, they reported:

- prevalence of severe obesity was greatest in black ♀ (20.1%) followed by black men (14%), white ♂ (11.7%) and white women (8.7%)
- BMI was significantly correlated between the two surveys for both sex and race groups.
- The frequency of hypertension was greatest in black females (13.9%) followed by black males (10.1%), white males (6.2%), and white females (5%).
- Significant correlations between time periods were found for both systolic blood pressure (SBP) and diastolic blood pressure (DBP) for both sexes and races except black females, aged 19-22y and DBP in black males aged 23-25 y.

- High total cholesterol was more prevalent in males than females; however, no differences by race were observed.
• Low levels of high-density lipoprotein-cholesterol (HDL-C) were more prevalent in white males than any other group.
• Black males had greater clustering of all three risk factors than the other groups.

Since the seminal report documenting gross lesions in coronary arteries of soldiers killed in action in Korea (Enos et al., 1986), an issue that has been the focus of much discussion has been the significance that such lesions, “fatty streaks,” have in the pathogenesis of CVD. Several large studies have been designed to document the ontogeny of these lesions. Berenson et al. (1998) expanded on their early reports of lesions in children and young adults, by evaluating the relationship between antemortem risk factors identified in previous examinations and the extent and nature of cardiovascular lesions found at autopsy in young adult participants in the Bogalusa Study. Among the findings were:

• “Essentially all persons in the age groups we studied, had fatty streaks in the aorta. In contrast, the prevalence of fatty streaks in the coronary arteries increased with age…”

• “The association between fatty streaks and fibrous plaques was much stronger in the coronary arteries than in the aorta.”

• BMI was the only factor significantly correlated with both fatty streaks and fibrous plaques in both the coronary arteries and aorta.

• SBP and LDL cholesterol were significantly correlated with fatty streaks in the aorta and both fatty streaks and fibrous plaques in coronary arteries.

• Total cholesterol was only associated with fatty streaks in aorta and coronary arteries but not fibrous plaques in either sites.

• DBP was only associated with fibrous plaques in coronary arteries.

• Serum triglycerides were associated with aortic fibrous lesions and with both fatty streaks and fibrous lesions in coronary arteries.

• Multiple risk factors were associated with an increase in intimal lesions in the aorta and to a lesser extent in the coronary arteries.

• Smoking history significantly increased the extent of fibrous lesions in the aorta and fatty streaks in the coronary arteries.

As with other reports from the Bogalusa Study, no diet data were included in these analyses.

As reviewed in Chapter 2 of this report, dietary data have been collected by the investigators involved in the Bogalusa Heart Study (Nicklas, 1995; Nicklas et al., 1993, 1995). However, the focus of the diet component of this effort has solely been on secular trends to the exclusion of attempts to test possible diet/disease or diet/risk factor associations (Berenson et al., 1998). Perhaps future analyses by this group will rectify this omission.
Another large-scale effort designed to assess the interaction between risk factors and pathogenesis of CVD is the Pathobiological Determinants of Atherosclerosis in Youth (PDA Y) Study (Malcolm et al., 1997; McGill et al., 1998; Strong et al., 1999; Wissler & Strong, 1998). As reviewed by Strong et al. (1999) the PDAY study was designed to “document the extent and severity of atherosclerosis in adolescents and young adults in the United States.” The outcomes measured in the PDAY study were intended to span the “transition from innocuous fatty streaks to clinically significant fibrous plaques,” and to determine “the conditions associated with this process.” The primary difference between the PDAY study and the Bogalusa Heart Study as reported by Berenson et al. (1998) was that in the former, the data on risk factors, e.g., blood lipid levels, were collected at the time of death, while in the latter, retrospective data were available from antemortem examinations of levels of risk factors.

In their summary of the data on the prevalence and extent of atherosclerosis in subjects in the PDAY study, Strong et al. (1999) itemized the following results:

- Intimal lesions (fatty streaks) appeared in all the aortas and more than 50% of the right coronary arteries of the youngest age group.

- Prevalence and extent of intimal lesions of coronary arteries increased with age.

- Fatty streaks were more extensive in black subjects than in white subjects, but raised lesions (fibrous plaques) did not differ between races.

- Although raised lesions were similar in aortas of both sexes, such lesions in the right coronary arteries of women were less extensive than those in men.

- The prevalence of total lesions was lower in the right coronary artery than in the aorta, but the proportion of raised lesions among total lesions was higher in the coronary arteries than in the aorta.

These authors concluded that atherosclerosis is a disease that begins in childhood, and consequently, interventions should begin at an early age. These recommendations were made in the absence of any data on diet, which presumably would be a focus of such interventions. As noted by the authors, this study was intended to describe the “transition from innocuous fatty streaks to clinically significant fibrous plaques...” (Strong et al., 1999). What was accomplished was a documentation of the existence of these innocuous streaks without a clear appreciation of when, under what conditions, and in whom these lesions develop into meaningful outcomes. The fact that the streaks appear in 100% of the aortas does not mean that 100% of these individuals would have developed CVD. Further, in the absence of any data on diet, demographics, family history etc., it is difficult at this time to assume that dietary interventions in early childhood is warranted on the basis of the existence of these lesions.

2. **Summary and conclusions**

Based on the studies reviewed in Table 5a, evidence exists to support the notion that risk factors associated with adult CVD appear in children. Racial, gender, and familial differences have all been associated with patterns of adverse risk factors in children. However, inconsistencies have been reported relative to individual risk factors. Specifically, levels of total cholesterol in children have not been consistently associated with risk in young adults. The most consistent factor associated with adverse CVD risk in both children and adults has been BMI. Other risk factors indicative of adverse risk such as circulating lipoproteins (high LDL and low
HDL) have been consistently reported. The prevalence, extent and nature of lesions to vasculature of young accident victims examined at autopsy have been described in several reports. Associations have been made between the extent and nature of these lesions and known risk factors such as circulating lipoprotein concentrations and BMI.

None of the studies reviewed in Table 5a included any data in the analyses on the relationship between the risk factors identified in children and adolescents and other environmental factors, including diet. Moreover, with the possible exception of excess weight gain/obesity, there are few data regarding risk factor levels in young prepubescent children. Consequently, although the evidence suggests that risk factors for CVD appear in children and adolescents, the link between diet and these risk factors can only be inferred from our understanding of the diet/CVD link in adults. Because of the absence of any data on this relationship in children, there appears to be little justification for dietary interventions in pre-pubertal children at this time.

C. TRACKING OF CVD RISK FACTORS

Table 5b includes several studies that have been designed to address specifically the issue of tracking of CVD risk factors from childhood to adult life. As with those studies that have confirmed the presence of adverse levels of risk factors in children, the tracking studies suffer from inconsistent results that may be accounted for by differences in design, sample characteristics, and analytical technique occurring between and within studies, as well as differences in criteria used to define "adversity." It does appear from the studies reviewed that temporal patterns exist with regard to most of the risk factors studied.

There has been mixed success with regard to the utility of childhood levels of risk factors as predictors of adult levels. For example, using data collected during the Bogalusa Heart Study, Bao et al. (1996a) demonstrated that undesirable levels of LDL-C (based on national standards for adversity established by the National Cholesterol Education Program; NCEP) persist from childhood to young adults. In another report from the Bogalusa study group, Myers et al. (1995) reported that "clustering" of risk factors (serum TC, systolic blood pressure [SBP], and BMI) had limited utility in predicting adverse levels in adults. In contrast, Lauer & Clarke (1990) reported that in the Muscatine study, TC was not a good predictor for those who would require interventions as adults. Of the children who had TC levels exceeding 75th percentile of the NCEP standard, 75% of girls and 56% of boys did not qualify for interventions as adults.

No consistent pattern has emerged. In fact, variables such as childhood levels of TC and HDL-C have not been statistically correlated with adult levels in several reports. Although the evidence derived from such studies as the Bogalusa Heart Study and the PDAY studies discussed above provide much useful evidence on the pathogenesis of atherosclerosis and CVD, none of that evidence was directly linked to diet. Again, the relationship between diet and the onset of aberrant risk factors in children is implied by evidence linking risk factors to diet in adults.

Of the studies reviewed, the only study conducted in children and young adults that included data specifically collected to assess the long-term relationship between diet and CVD risk factors was the Amsterdam Growth and Health Study (Post et al., 1997; Twisk et al., 1997). The results from this study raise more questions than they answer. For instance, Post et al. (1997) reported a negative association between body weight and energy intake. Twisk et al. (1997) reported "no relationship" between the dietary intake of macronutrients and CVC risk factors.
In summary, although evidence suggests that many of those factors that have been associated with adult CVD appear in children and adolescents, the utility of monitoring the levels of many of these factors in pre-pubescent children, in order to predict individuals at risk for adult disease has not been firmly established. An additional consideration is the potential for adverse outcomes such as the psychosocial concerns identified by Rosenberg et al. (1997) consequent to labeling young children as high risk based on such screening practices. In light of the absence of many of the other variables that may influence the occurrence and severity of the CVD risk factors, e.g., diet, family history, demographics, in the analyses presented it would appear to be premature to commit to this practice at this time.

D. HYPERTENSION

The importance of hypertension to the pathogenesis of CVD disease and particularly atherosclerosis is indicated by the findings of the PDAY investigators, who observed that "hypertension augments atherosclerosis in both men and women primarily by acceleration of the conversion of fatty streaks to raised lesions beginning in the third decade of life, and the effect of hypertension increases with age." Clearly, the question is in whom is this risk most apparent and can we predict this risk based on measurement of BP in children? Based on the review of the studies in Table 5c, the answer to this latter question is maybe.

Although the majority of the studies reviewed examined temporal associations between BP and other risk factors in youth and into adulthood, few actually focused on clinically diagnosed essential hypertension. Several studies including the Bogalusa Heart, the Muscatine Iowa, and the PDAY studies have been designed to provide evidence of tracking of BP, and most results are indicative of a predictive value, particularly for systolic blood pressure (SBP). However, other studies, such as the Tecumseh, Michigan study are less supportive of the use of childhood BP to predict adult risk. The most important finding of the Tecumseh study is supportive of the majority of studies investigating the link between BP and other risk CVD risk factors, i.e., that body size and family history are perhaps the most important factors related to clinically adverse levels of BP.

Few studies have addressed the potential link between diet and nutrient intake and BP in children. Data from the Sodium-Potassium Blood Pressure Trial in Children are indicative of a relationship between circulating levels of specific fractions of calcium; however, no association with dietary intake was observed in this cohort. In contrast, the investigators in the Dietary Intervention Study in Children (DISC) study (Simons-Morton et al., 1997), reported significant inverse associations between dietary intake of micronutrients (calcium, magnesium, potassium and protein) and BP, and a positive association between dietary fats and BP in a selected sample of children with high levels of LDL-C.

Again, although some of the available evidence indicate a long-term pattern of BP, the relationship of this pattern to factors that might be considered in a dietary intervention in children is not yet clear.

E. OBESITY

As seen in Table 5d, BMI, which is used as the default marker for adiposity, has been strongly, consistently, and independently associated with adverse CVD risk during childhood, over the course of development to adulthood and in adults. In addition to association with pathological lesions of coronary vasculature, BMI has been linked to the primary biochemical CVD risk factors, i.e., elevated LDL-C and reduced HDL-C. The
pattern of weight gain over time may be a greater concern than the BMI value at any given time. As demonstrated in the report of the Minnesota Children's Blood Pressure Study (Sinaiko et al., 1999) weight gain through childhood to adulthood may be a more significant predictor of risk than a single measure of weight and consequently, prevention of excess weight gain rather than weight loss might be a more effective intervention strategy.

The importance of weight gain was emphasized in several reports, including the Bogalusa Heart Study (Gidding et al., 1995), in which the significant association between secular trends in weight gain and CVD risk factors was demonstrated. Again, as noted for all of the other aspects of the relationship between childhood antecedents of adult CVD, the absence of any data with regard to the role of diet in the development and maintenance of adverse levels of BMI makes discussion of specific dietary interventions in children premature. Furthermore, in light of the evidence, the question of the type, weight loss versus prevention of excess weight gain, and timing, pre- or post-adolescence, of such intervention remains unresolved.

F. IMPACT OF INTERVENTIONS TO REDUCE CVD RISK IN CHILDREN

Despite the vast amount of evidence linking adult dietary patterns to risk factors for adult CVD, there remains little but inference to support dietary interventions in children. Yet, the desire to protect children from the onset of these disabling diseases has driven much of the debate in the national nutrition policy arena. Based on reports of adverse effects concerns consequent to the unsupervised implementation of diets intended to reduce CVD risk factors in children (Lifshitz & Moses, 1989) safety of such interventions has become a focal point of concern. Consequently, a number of studies have been designed to address the safety and efficacy of dietary interventions in children and are summarized in Table 5e.

The largest trial designed specifically to address the safety and efficacy of an intervention for the reduction of a putative CVD risk factor in children has been the Dietary Intervention Study in Children (DISC) (DISC Collaborative Research Group, 1993). The objective of this multi-center prospective intervention trial was to “assess the efficacy and safety of a lipid-lowering diet in 8 to 10-year old children with moderately elevated LDL-C.” The study involved a total of 663 children divided into an intervention group (n=334) and a usual care or control group (n=329). The groups were matched at baseline for gender, age, mean LDL-C, normal dietary intake, anthropometric measures (height, weight, BMI, and skinfold thickness from three sites), and BP. The DISC Research Group (DISC Collaborative Research Group [The Writing Group], 1995) reported a modest difference in the decrease in LDL-C between the two groups in the absence of any differences in growth or serum ferritin (the other major dependent variable). This study also provided confirmation of other reports of the developmental changes in LDL-C levels (Srinivasan & Berenson, 1995). In pubertal children, sexual maturation, BMI, dietary interventions (in girls), and dietary cholesterol (in boys) were significant determinants of LDL-C. “Sexual maturation was the factor associated with the greatest difference in LDL-C” (Kwiterovich et al., 1997).

It should be noted that the use of low fat diets were not without consequence. Lower fat intake was associated with higher levels of red blood cell folate and hemoglobin, higher intakes of folate, vitamin C, and vitamin A, lower intakes of calcium, zinc, magnesium, phosphorus, vitamin B12, thiamin, niacin, and riboflavin, increased risk of consuming less than 2/3 of the RDA (NRC, 1989) for calcium in girls at baseline, and zinc and vitamin E in both genders at all visits (Obarzanek et al., 1997). Given the extent and nature of these dietary findings, it would appear that the study could have benefitted from an analysis of foods groups in addition to the
individual nutrient assessments. Such an analysis might have shed light on which foods contributed to these effects and allowed for a more effective evaluation of the efficacy of this and subsequent interventions.

The finding of increased risk for reduced calcium intake is particularly disturbing and has been reinforced by the report by Johnson & Wang (1997) who documented reduced calcium intake in children consuming low versus high fat diets. The risk for lower intakes of several essential nutrients, including calcium, was dismissed by the authors because “no adverse effects were observed on blood biochemical measures of nutritional status.” However, no biochemical assessments of vitamin B12, thiamin, niacin, or riboflavin were performed. Further, there were no assessments of bone density or any other measures of bone health that are critical in the evaluation of the impact of dietary calcium, a significant issue particularly in adolescent girls (see Chapter 7 of this report). Finally, as reviewed in Table 5c, Simons-Morton et al. (1997) reported significant inverse associations between dietary intake of micronutrients (calcium, magnesium, potassium, and protein) and BP in the DISC cohort, adding additional concern with regard to the potential harm from reduced intakes of these essential nutrients.

Several other studies have been conducted to evaluate the impact of dietary interventions in children. The Child and Adolescent Trial for Cardiovascular Health risk (CATCH) study involved a comparison of three treatments: an intense school-based education diet and health intervention plus physical education (the CATCH intervention), the CATCH intervention plus a home-based education program, and the standard school-based health education curriculum (control group) (Edmundson et al., 1996). A total of 96 elementary schools participated in this study. Subjects were randomized into the three treatment groups (total n= 7,795; mean age at baseline 8.75 y). The dependent variables in this study were psycho-social factors which “...influence behavioral risk factors (dietary, physical activity, smoking) which influence physiological risk factors (blood lipids and blood pressure) which determine morbidity and mortality.” Edmundson et al. (1996) reported “sustained significant effects in improved knowledge, intentions, self-efficacy, usual behavior, and perceived social reinforcement for healthy food choices after three years.” These authors concluded that “The CATCH program was effective in changing the psychosocial variables likely to influence a reduction in behavior for CVD.” None of the endpoint risk factors (e.g., blood lipids) or actual dietary intake were included in this report.

Other groups have reported no adverse effects from dietary intervention (specifically designed to reduce levels of putative CVD risk factors in children and have concluded that no safety concerns exist with regard to these treatments (Table 5c). Jacobson et al. (1999) reported that they successfully implemented the NCEP Step 1 diet (total fat intake less than 30% of total calories, less than 10% of total calories as saturated fat, and less than 100 mg cholesterol/1000 kcal/day) in a “convenience” cohort of 138 children ranging in age from 2 to 15 years. After three years, TC was significantly reduced compared to baseline levels.

A number of issues place limitations of the interpretation and generalizability of these results.

- This was an unblinded observational study of a self-selected “convenience sample” without the benefit of a comparison group. The authors acknowledged that “the study group was a sample of convenience, reviewed retrospectively by chart audit, and thus was not randomly selected or population based. Combining patients from three sites poses problems with comparability of methods and data.”
- Dietary intake data, either at baseline or at any point of the intervention, were not presented, discussed, or included in the analyses.
The appropriateness of the authors’ unorthodox use of the dependent variable, TC, to establish compliance might have been tested by evaluating the diets of these subjects.

No analysis or control for gender or age was included in these data. There was an apparent interaction with age as evidenced by the larger changes in lipid profiles occurring in older children (>10 y). The pattern of change were consistent with those age-dependent changes described in previous studies (Srinivasan & Berenson, 1995).

Based on these limitations, the authors reserve in restricting their conclusion about the safety of this intervention to “no demonstrable adverse effect on growth,” was clearly appropriate.

A similar intervention study was conducted by Tershakovec et al. (1998) in which growth as reflected by changes between treatment groups over a three-year period was assessed in 261 hypercholesterolemic (TC greater than 176 mg/dL; 75th percentile) children between the ages of 3.9 and 9.9 years. After initial TC screening, candidate subsequently evaluated for LDL-C concentrations. Those meeting the study criteria (LDL-C 107 to 164 mg/dL for boys, 112 to 164 mg/dL for girls) were randomized into three study groups: 2 nutrition education interventions and an “at-risk” control group. An additional “not-at-risk” control group was selected from children without elevated TC (less than the 60th percentile). Anthropometric measures (height, weight, 4 sites for skinfold measurement), BP, and TC were measured at 3, 6, and 12 months after initiation of the interventions. Three 24-hour diet recall, (2 weekdays and 1 weekend day) were collected at each evaluation. The dependent variables did not include changes in blood lipids. Again, the intervention resulted in significant reduction intake of total and saturated fat, without an untoward impact on linear growth. However, not only was there no data or analysis on the efficacy of the intervention in terms of reduction of the putative risk factor (TC or LDL-C), there were no assessments of other nutrients that might have been negatively affected by this intervention. Consequently, while Tershakovec et al. (1998) confirmed a lack of an effect on linear growth, their study was not designed to test efficacy or to rule out the potential for other adverse dietary and nutritional effects.

In conclusion, while the efficacy of educational interventions has been confirmed in several reports, safety concerns remain. We know that we can reduce the levels of putative risk factors in children, the more important unanswered questions are when and/or whether we should.
Table 5a: Studies of Cardiovascular Disease (CVD) Risk Factors in Children

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Subject Number and Description</th>
<th>Methods Outcome Variables</th>
<th>Results and Authors' Conclusions</th>
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<tr>
<td>Berenson et al., 1998</td>
<td>Autopsies were performed on 204 young people (86 white σ, 52 black σ, 36 white ι, 30 black ι). Of these, 93 (41 white σ; mean age 19.6 y, 23 black σ; mean age 21.7 y, 19 white ι; mean age 20.4 y, and 10 black ι; mean age 22.4 y) had been previously evaluated as part of the Bogalusa Study and were the focus of this report.</td>
<td>This study was designed to examine “the influence of multiple risk factors on the extent of atherosclerosis in the aorta and coronary arteries in young people.” In addition to the clinical data obtained during previous examinations, autopsies were performed at death and tissue samples from the aorta and coronary arteries were obtained. All samples were examined independently by three pathologists. “The extent of atherosclerosis was expressed as the mean of the three values assigned by these pathologists for the percentage of the intimal surface covered by lesions.” For the 65 persons whose risk factor status was assessed more than once, the average of the age, sex, race-adjusted levels were used. “Risk factors were defined as values above the 75th percentile (specific for study period, race, age, and sex) for the group as a whole.”</td>
<td>“Essentially all persons in the age groups we studied, had fatty streaks in the aorta. In contrast, the prevalence of fatty streaks in the coronary arteries increased with age...” “The association between fatty streaks and fibrous plaques was much stronger in the coronary arteries than in the aorta.” - BMI was the only factor significantly correlated with both fatty streaks and fibrous plaques in both the coronary arteries and aorta. - SBP and LDL cholesterol were significantly correlated with fatty streaks in the aorta and both fatty streaks and fibrous plaques in coronary arteries. - TC was associated only with fatty streaks in both aorta and coronary arteries. - DBP was associated only with fibrous plaques in coronary arteries. - serum triglycerides were associated with aortic fibrous lesions and both kinds of lesions in coronary arteries. - Multiple risk factors (clusters) were associated with an increase in the extent of intimal lesions of the aorta and to a lesser extent in the coronary arteries. - Smoking history significantly increased the extent of fibrous lesions in the aorta and fatty streaks in the coronary arteries.</td>
<td>No data on demographics, family history, or diet were included in these analyses. Data were presented by age groups, but n’s in each group were not provided. Moreover, in the presentation of the results of those analyses that did not include antemortem data, i.e., prevalence and age correlations of lesions, it was not clear whether the data represented all 204 subjects on whom autopsies were performed, or only the 93 who had previously been examined. The extent of agreement between the three pathologists was not reported. The time of collection of the clinical values relative to death was not evaluated. (As noted, 65 subjects had multiple evaluations, presumably that meant 28 had only one evaluation).</td>
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<td>Wattigney et al., 1995</td>
<td>The Bogalusa Heart Study involved collection of dietary and clinical data from 6 cohorts of 10 year-olds (n=1,439) and 2 cohorts of 13 year-olds (n=360) from a bi-racial (black and white) community. Additional cohorts of infants 6 months to 4 years and again at 10 years were collected, as well as a cohort of 10 to 17 year-olds who were assessed biannually. This study evaluated data from - 1,928 young adults (ages 19-32) examined in the 1988-1991 survey - 1,587 subjects originally evaluated as children in the 1973-1974 survey.</td>
<td>Examination protocols for all subjects were identical in all surveys and included: collection of fasted blood samples (to be analyzed for lipids and lipoproteins) followed by a simple meal, anthropometric measures (height, weight, calculated BMI), routine physical exam, 9 BP measurements (hypertension was defined as SBP &gt;140 mmHg, DBP &gt;90 mm Hg or positive response to the question of treatment for high BP), health habits questionnaire (third grade and higher) and for young adults in the 1988-1991 survey only, a medication interview. &quot;overweight&quot; = ≥BMI 27.8 for σ, 27.3 for η and &quot;severe overweight&quot; = ≥ 31.1 and 32.3 for σ and η, respectively. Prevalence was determined by sex and race.</td>
<td>Obesity: - prevalence of severe obesity was greatest in black η (20.1%) followed by black σ (14%), white σ (11.7%) and white η (8.7%). - BMI was significantly correlated between the two surveys for both sex and race groups. BP: - frequency of hypertension was greatest in black η (13.9%) followed by black σ (10.1%) white σ (6.2%) and white η (5%). - significant correlations between time periods were found for both SBP and DBP for both sexes and race except black η aged 19-22y and DBP in black σ aged 23-25 y. “Year 1 to year 15 association were consistently stronger for systolic levels than for diastolic levels...” Blood Lipids: - high TC was more prevalent in σ than η. no difference by race. - low HDL-CI was more prevalent in white σ than any other group Clustering of Risk Factors: - black σ had greater clustering of all three risk factors than the other groups.</td>
<td>- No diet data presented in this report. - Data were presented by age groups in the 1988-1991 survey. No similar data were presented for ages of those who participated in the first survey. Although BMI and blood pressure were significantly correlated between the two examinations (15 y period), the prevalence of overweight or severe overweight or high BP was only reported for the young adults. “Persons were classified as hypertensive primarily due to reported treatment...” “Relatively few” actually had hypertension by BP. No analyses for lifestyle or demographic factors included in this study.</td>
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<td>Lauer &amp; Clarke, 1990</td>
<td>A total of 2367 subjects participated in both phases of this protocol and were included in the analyses. In the first phase (1971-1981) schoolchildren aged 5-18 were screened during 6 biennial surveys. Individuals who participated in any of the six surveys were reexamined between 1981-1985 when they were 20-30 years of age.</td>
<td>This study was designed to test the validity and utility of screening tests for total cholesterol concentrations in school-aged children to predict those who will have levels &gt;200 mg/dL as adults. Sampling procedures were identical in all surveys. 12-hour overnight fasted blood samples Subjects were grouped according to age and gender specific percentiles rather than absolute levels. The percentiles were based on cholesterol levels of participants in the Muscatine study. (n=10,160 individuals, 19,006 observations) Sensitivity was defined as “percentage of adults with levels of cholesterol greater than or equal to 200 mg/dL. (True positive)” Specificity was defined as the number of individuals with cholesterol levels &lt; 200 mg/dL. (True negative) Predictive value was the percentage of children with positive criteria who became adults with cholesterol levels &gt;200 mg/dL.</td>
<td>At a criterion of &gt;75th percentile the sensitivity was 45% and specificity was 90% for both genders. For ß the positive predictive value was 45% and negative predictive value 89%; corresponding positive and negative predictive values for ß were 57% and 86%, respectively. Using a criteria of &gt;90th percentile the sensitivity was 16% for ß and 21% for ß. Specificity was 98% for both genders. The predictive value of a positive test was 75% for both genders. Predictive value for a negative test was 81 and 87% for ß and ß, respectively. “Of children with cholesterol concentrations exceeding the 75th percentile on two occasions 75% of girls and 56% of boys would not qualify for intervention as adults by the National Cholesterol Education Program criteria. Of children with cholesterol levels exceeding the 90th percentile on two occasions, 57% of girls and 30% of boys would not qualify for intervention as adults.”</td>
<td>“No interventions were provided,” except for 21 children in the 95th percentile or greater who were told they had high cholesterol. The mean cholesterol levels of the adult age and gender groups ranged from 172 to 182 mg/dL. As these levels are relatively low, it would have been useful to have a control sample of aged matched adults who had not participated in the Muscatine study to control for the effects of involvement.</td>
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<td>Malcolm et al., 1993</td>
<td>Children ages 6-14 were recruited from the schools of Muscatine, Iowa between 1987 and 1989. Of the 925 examined, the final data set was 904 (452 ♀, 452 ♂). No specific inclusion criteria. None of the subjects had CVD or were taking medications.</td>
<td>Increased left ventricular mass (LVM) is a cardiomyopathy associated with adverse outcome. This study was designed to assess the relationship between body size, age, and BP and LVM and to generate normative data for LVM. Measurements include height, weight, calculated BMI, SBP, DBP, and ultrasound imaging of the heart (echocardiogram). Correlation coefficients were calculated to describe relationship between LVM, age, body size, and BP. Gender-specific LVM prediction equations were computed. Z scores were used to divided subjects into quintiles for comparison. High LVM was the highest age-sex, height-sex, or weight-sex specific quintile. Of the 925 children examined 19 had unacceptable echocardiograms and 2 were missing weight data.</td>
<td>&quot;A strong positive linear association&quot; of LVM with age, weight, height, BMI. Although statistically significant the association was weaker for SBP and weakest for DBP. &quot;... age, height, weight, and BP each exert an independent influence of LVM in children.&quot; &quot;While age, sex, and height are unalterable, both weight and BP can be modified. Thus, the pathologic contributions of excess weight and BP ought not be masked by statistical adjustments in reference values for LVM.&quot;</td>
<td>No family history, demographic (including race), or diet data included in this analysis.</td>
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<td>Muhonen et al., 1994</td>
<td>A three-stage process led to the constitution of the study sample. Target sample: 1) 1024 (549 female, 475 male) high school students (ages 14-20 years) were asked to complete a family health history questionnaire. 2) 741 (72%) of the target filled out “at least some portion” of the questionnaire and were asked to participate in a school-based examination. 3) 599 students (58% of the target, 301 female, 298 male; mean age 15.6 years, 298 female, mean age 15.8 years, 91% non-Hispanic white) completed both the questionnaire and the examination.</td>
<td>The objective was to use a school-based family history questionnaire to identify adolescents with adverse coronary risk factor levels. <strong>Questionnaire:</strong> administered to all students enrolled in Muscatine high school science classes. Students took them home to complete questions about first degree (parents and siblings) and second-degree (grandparents, aunts/uncles) relatives. Asked about heart attacks, angina, bypass surgery, high BP, high cholesterol, and obesity. Data for parents and grandparents only used in this report. <strong>Examination measures:</strong> height, weight, calculated BMI, triceps skinfold thickness (TSF), BP (average of three readings), fasted (overnight) blood samples collected for the assessment of TC and HDL-C, and TG.</td>
<td><strong>Cholesterol:</strong>  - &quot;Although total, LDL-C, and apoB were increased in students with a parental history of high cholesterol, they were not significantly higher than levels of students in the negative or unsure groups.&quot;  - students with a positive grandfather history for high TC had significantly greater TC and LDL-C, LDL-HDL ratios, and apoB levels than students w/o histories.  - no difference found based on grandmother history. <strong>CVD:</strong>  - Risk of being in the highest decile of BMI and lowest decile of apoA1 are increased significantly in students with positive parental history of early-onset CVD.  - grandfather with early or late onset CVD was associated with increased BMI and TSF.  - DBP was higher, apoA1 lower, and tendency towards lower HDL in students with grandfather with early onset CVD.  - odds of being in upper decile of BMI and SBP and lower decile of apoA1 were greater when grandfather had positive early CVD  - positive late CVD in grandfather also associated with increased risk of upper decile of BMI, SBP and lower HDL-chol.</td>
<td>Actual BP, blood lipid, or anthropometric data for relatives were not collected. Large percentages of students had incomplete family histories with respect to the risk factors being studied. For example, 26% of students were classified as having an unsure parental history of high cholesterol, 45% couldn’t classify grandfathers’ cholesterol history, despite 70% of students having some data for both grandfathers. &quot;The positive predictive values associated with using a school-based history obtained from adolescents, many with the aid of their parents, are small and many adolescents do not know their family history.&quot;</td>
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<td>McGill et al., 1998</td>
<td>See Strong et al., 1999</td>
<td>This is a summary of the PDAY study which was a cross sectional study involving 15 clinical centers throughout the U.S., and designed to examine the relationship of risk factors for adult coronary artery disease to atherosclerosis. Right coronary arteries, abdominal and thoracic aortas, blood (samples were collected and then stored at -80° C) and kidney samples were collected from all victims. Tissue samples were rated independently by three pathologists to determine the extent and nature of the observed lesions. The mean of the 3 ratings was used for data analysis. Risk factors evaluated were: VLDL, LDL and HDL cholesterol, smoking (determined based on level of thiocyanate in serum), diabetes and impaired glucose tolerance (based on level of glycosylated hemoglobin [Hgb] in red blood cells),BMI (measured at autopsy), hypertension (based on intimal thickness of renal artery and an algorithm to estimate mean arterial pressure).</td>
<td>After adjusting for lipoprotein cholesterol and smoking, extent of fatty streaks in the coronary arteries increased linearly with age. - VLDL and LDL levels were positively associated and HDL negatively associated with fatty streaks particularly after age 25. - Ghb was positively associated with more extensive coronary artery fatty streaks - BMI was associated with fatty streaks in σ but not γ. - Neither smoking or hypertension affected coronary fatty streaks. Raised plaques were positively associated with VLDL, LDL, Ghb, BMI (in σ), smoking (in the abdominal aortas of 25-34 y age group). “The risk factors for adult coronary artery disease accelerate atherogenesis in the teenage years and their effects are amplified in young adulthood, 20-30 years before coronary artery disease becomes clinically manifest. Long-range prevention of adult coronary artery disease will require control of the risk factors early in life.”</td>
<td>No demographic data, family history or diet history available for these victims. Although not discussed in this paper, the post-mortem effects on the samples used in this analysis were presumably accounted for in previous studies. Similarly, the timing between death and sample collection particularly for blood samples was not discussed.</td>
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<td>Rainwater et al., 1999</td>
<td>See McGill et al., 1998; Strong et al., 1999</td>
<td>The focus of this report was on the relative utility of serum lipids versus apolipoproteins, i.e., the characteristic protein components of individual lipoprotein, in the prediction of atherosclerosis using the PDAY study sample. The specific focus was on apoA1, apoB and Lp(a) compared with HDL cholesterol and non-HDL cholesterol (traditional lipid measures). See McGill et al. (1998) for further details on methodology.</td>
<td>The apolipoprotein measures were not &quot;as strongly or consistently correlated with the extent of lesions...&quot; as the traditional lipid measures. After controlling for the effects of age, sex, race, smoking, and hypertension, the addition of apolipoproteins accounted for 1.3% of the variation in lesions. &quot;The results suggest that the traditional lipid measures are more useful than apolipoprotein measures for detecting young persons at high risk of precocious atherosclerosis.&quot;</td>
<td>See McGill et al., 1998</td>
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<td>Strong et al., 1999</td>
<td>Study subjects were individuals aged 15-34 y of age who had died due to external causes and underwent autopsy. A total of 3210 cases were collected. 334 were excluded. 2856 (1008 white σ, 1151 black σ, 367 white ῶ, 330 black ῶ) cases included in this report.</td>
<td>The focus of this summary paper was on the “extent, prevalence, and topography of atherosclerotic lesions” in young black and white persons ages 15-34. (See McGill et al., 1998)</td>
<td>- Intimal lesions (fatty streaks) appeared in all the aortas and more than 50% of the right coronary arteries of the youngest age group. - Prevalence and extent of intimal lesions of coronary arteries increased with age. - Fatty streaks were more extensive in black subjects than in white subjects, but raised lesions (fibrous plaques) did not differ between races. - Although raised lesions were similar in aortas of both genders, such lesions in the right coronary arteries of women were less than those in men. - The prevalence of total lesions was lower in the right coronary artery than in the aorta, but the proportion of raised lesions among total lesions was higher in the coronary arteries than in the aorta. &quot;Atherosclerosis begins in youth. Fatty streaks and clinically significant raised lesions increase rapidly in prevalence and extent during the 15-34 y age span. Primary prevention of atherosclerosis, as contrasted with primary prevention of clinically manifest atherosclerotic disease, must begin in childhood or adolescence.&quot;</td>
<td>No data were presented on children less than 15 years. Consequently, it would be premature based on these data to suggest interventions in childhood.</td>
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| Amsterdam Growth and Health Study  
(Post et al., 1997; Twisk et al., 1996; 1997) | 182 subjects (98 females, 84 males) mean ages 13 at the start of the study in 1977 and 27 in 1991, the last of the six study periods. | Objectives:  
- Post et al. (1997) focused on the relationship between dietary patterns and CVD risk factors (total cholesterol (TC), HDL, BP, body fat (sum skinfold measures from 4 body sites), maximal aerobic power (VO₂ max)  
- Twisk et al. (1997) explored potential associations between macro-nutrient intake, smoking, alcohol consumption, and daily physical activity and CVD risk factors (lipoproteins, BP, body fatness).  
- Non-fasting blood samples were collected and utilized in those studies examining associations involving blood lipids  
- Dietary measurements were collected a total of 6 times over 15 year period; annually over the first four years (ages 13-17), once each at ages 21 and 27.  
- A food frequency/dietary history interview was used with a one month reference period. Parent/caregivers were questioned about qualitative details, e.g., skim vs whole milk etc.  
Post et al. (1997) reported "borderline or high CVD risk values” (body fat and TC) in more than 25% of 27 y old. Significant positive associations were observed between intakes of animal protein, saturated fat, cholesterol, and blood levels of TC and HDL, between total energy intake and SBP and VO₂ max and negative associations between intakes of energy, polyunsaturated fat and blood TC and energy intake and body fat.  
Twisk et al. (1996) found that tracking over the 15 year study period was significant for TC, HDL-C (greater in Σ than Ψ), and for the TC:HDL-C ratio. Tracking was more significant for TC and the ratio of TC:HDL-C than for HDL-C. Changes in TC were positively associated with body fatness and daily exercise. TC:HDL-C ratio was positively affected by body fatness at 13 y of age. No associations were observed between HDL-C and any of the other factors measured.  
Twisk et al. (1997): smoking was inversely related to HDL-C and positively associated with TC; smoking and alcohol were inversely related to BP. “No relationship was found between the dietary intake of macronutrients and CVD risk factors.” The tracking of “the dietary parameters [protein, fat, and carbohydrates] over a 15-year period was quite low.” Particularly compared to the tracking of serum TC. | The use of only 6 retrospective measures of intake over a period of 15 years might have limited the validity of these data sets  
Post et al. (1997) commented that the negative associated between energy intake and body fat was "partly explained by the relation between energy and VO₂ max." |
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<td>Bao et al., 1996a</td>
<td>See Wattigney et al., 1995</td>
<td>This report included data collected to address the use of LDL-C levels in children to predict CVD risk factors in adults.</td>
<td>BMI at baseline was significantly associated with follow-up levels of TC, triglycerides, and HDL-C. No statistically significant regressions were found between baseline and follow-up levels of any of the blood lipid measures. Age was positively associated with triglyceride levels and negatively associated with HDL-C. Adult levels comparable to NCEP standards for dyslipidemia were best predicted by childhood LDL-C levels compared to other blood constituents. Subjects with high childhood risk for LDL-C based on NCEP standards (6% of those studied) for children “not only had a higher prevalence of dyslipidemic TC (24%), LDL-C (28%), TG (7%), and lower HDL-C (14%) but also had a significantly higher prevalence of obesity (43%) and hypertension (19%).” “Adverse levels of LDL-C in childhood persist over time, progress to adult dyslipidemia, and relate to obesity and hypertension as well.”</td>
<td>No diet or family history data included in these analyses. The authors mentioned the “variability in cholesterol measures,” however, actual mean and standard errors/ deviations were not presented.</td>
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<td>Bao et al., 1997</td>
<td>See Wattigney et al. (1995) and Bao et al. (1996a)</td>
<td>The objective was to “examine the association between parental coronary artery disease (CAD) and longitudinal changes in risk factor profile” in their offspring. (See Bao et al., 1996a)</td>
<td>BMI of subjects with parental history was significantly &gt; at all time points than those without parental history. At baseline (1973-1974) subjects with parental history were older, weighed more, and had a greater BMI than those without history.</td>
<td>No diet or demographic data. The independent variables were limited to age, race, sex, and differences in levels of risk factors between surveys. With regard to the latter, “the differences represented secular trend or possible laboratory drift.” Other than history of CAD no other data from parents, e.g., BMI, BP, blood lipids, were included in these analyses.</td>
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<td>Subjects in the 1988-1991 follow-up survey were asked about parental history of coronary artery disease (CAD). Parental history was confirmed via contact with surviving relatives. Subjects with a falsely reported parental history, non-biological parents, or an unverified parental history were excluded. History of parental CAD was verified in 271 individuals (230 had 1 parent, 41 had history in both parents). 1253 individuals in the follow-up study were also included in these analyses</td>
<td>Verification parental history was obtained via telephone interviews with either the surviving parent or next of kin during the period of 1994-1995 (3-4 years after the follow-up study with the subjects). In addition to age of onset and/or remedial procedure, questions included history of myocardial infarction, angina pectoris, angioplasty, bypass surgery, or medications. Biological relationship was also confirmed. Statistical design included the use of a repeated measures regression analysis.</td>
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<td>Myers et al., 1995</td>
<td>See Wattigney et al. (1995)</td>
<td>This paper included analyses to explore the childhood characteristics of adult subjects in both clustered and non-clustered groups and to develop a logistic model to predict adult levels from childhood levels of serum TC, HDL-C, glucose and insulin than those without parental history. “...the prevalence of dyslipidemia, either involving LDL-C singly or in combination with HDL-C or TG or both was significantly higher in the adult offspring with parental CAD.”</td>
<td>After controlling for sex, age, and race, a significant association was observed in children between BMI and TC and between BMI and SBP. Of children who placed in the top quartile on three factors (n=136, 3.7%), i.e., were clustered, 21.8% were clustered as adults. Only 1.1% of those with no risk factor levels in the top quartile as children were clustered as adults. Of the subjects in both surveys (n=1457). 58 (4%) were clustered as adults. BP was the best predictor.</td>
<td>See Bao et al., 1996a, 1997; Wattigney et al., 1995</td>
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<td>This study included three groups: from the baseline survey (1973-1974); 3,633 subjects (mean age 10.2 y, 62.8% white, 47.4% *)</td>
<td>This paper included analyses to explore the childhood characteristics of adult subjects in both clustered and non-clustered groups and to develop a logistic model to predict adult levels from childhood levels of serum TC, HDL-C, glucose and insulin than those without parental history. “...the prevalence of dyslipidemia, either involving LDL-C singly or in combination with HDL-C or TG or both was significantly higher in the adult offspring with parental CAD.”</td>
<td>After controlling for sex, age, and race, a significant association was observed in children between BMI and TC and between BMI and SBP. Of children who placed in the top quartile on three factors (n=136, 3.7%), i.e., were clustered, 21.8% were clustered as adults. Only 1.1% of those with no risk factor levels in the top quartile as children were clustered as adults. Of the subjects in both surveys (n=1457). 58 (4%) were clustered as adults. BP was the best predictor.</td>
<td>See Bao et al., 1996a, 1997; Wattigney et al., 1995</td>
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<td>Follow-up survey group (1988-1991): 1,864 (mean age 26.2y, 68.2% white, 55.4% *)</td>
<td>Clustering was done by placing individuals with values in the upper quartile of each of the three risk factors. See Wattigney et al., 1995</td>
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<td>Combined survey: 1,457 subjects were screened at both follow-up and baseline.</td>
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* Mean age 10.2 y, 62.8% white, 47.4% ; Mean age 26.2y, 68.2% white, 55.4%; Average follow-up interval was 15.7 y.
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<td>Adelaide Nutrition Study</td>
<td>The subjects were drawn from the Adelaide Nutrition Study in Australia. Subjects (n=106) were recruited at birth and followed through age 15 y. An additional group (n=123) were added beginning at age 11; also followed through age 15 y.</td>
<td>This report includes data from a larger study on tracking of risk factors for ischemic cardiovascular disease. Tracking was defined as &quot;the correlation coefficient between age points, e.g., 2-8 y, 2-11 y...&quot; In addition to fasted blood samples collected at 1 and 2 years of age and annually thereafter, 4 day weighed food records (3 weekday, 1 weekend) were collected annually. Two different databases were used for nutrient analysis over the course of the study.</td>
<td>&quot;For mean daily energy, fat and calcium intake, tracking coefficients were low below 4 years of age, but from then on were 0.46-0.64 for energy intake, 0.38-0.51 for fat (g) and 0.51-0.62 for calcium (mg).&quot; Tracking was similar for $\sigma$ and $\varphi$. Tracking for total cholesterol and LDL was higher as the children grew older. Correlations were less for HDL cholesterol. &quot;Tracking of dietary calcium was stable between intervals from 4 years of age, but there was a greater degree of continuity from 6 to 11 years onwards and from 8 to 11 years onwards than for energy or fat, particularly for males. There was an equal degree of drift downwards for those in the top quintile at 4-8 and 8 and 15 years of age as there was upwards for those in the bottom quintile for both absolute calcium intake and calcium density (mg/mJ).&quot; All time periods for which there were data, i.e. &gt; 4 y, were positively correlated (p&lt;0.001)</td>
<td>A comparison of the two nutrient databases revealed &quot;minor differences&quot; in calculations for fat content which &quot;would not have affected the outcome of the tracking.&quot; Actual data were not provided.</td>
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<td>Basel, Switzerland (Mohler et al., 1996)</td>
<td>Subjects were a randomly selected sample ( (n=375) ) of 5 y old Swiss and Italian children from Basel, Switzerland. All subjects were born in Switzerland. 126 subjects (34%) were lost to follow-up 9-y follow up data were available for 249 children (66%; 218 Swiss, 31 Italian). An additional 147 subjects were at the age of 10 to increase the number of subjects.</td>
<td>Examination took place at school and included anthropometrics measures (height, weight, calculated BMI), BP and collection of non-fasting blood samples (all samples collected at the same time in the AM). Biochemical measures included TC, LDL, VLDL, HDL.</td>
<td>No significant tracking correlations were found for TC over the 5 and 9-y periods. Gender and ethnic (Swiss versus Italian) differences were noted for tracking of LDL and HDL. TC:HDLC tracked best for Italian 9. “Individual changes in TC between the ages of 5 and 14 were marked.” “BMI was the most consistent risk factor in our population.”</td>
<td>Methods of biochemical assessment changed over the course of the study. No diet data collected. No analysis using demographic or family data.</td>
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<td>Fels Longitudinal Study (Guo et al., 1993)</td>
<td>96 white participants in the Fels Study. Data used in this report were from samples collected annually from subjects between the ages of 9 and 21 y.</td>
<td>This study had two objectives 1) determine the tracking coefficients between pairs of serial measures of plasma lipids and lipoproteins from childhood to adults. 2) determine whether childhood values predict the probability of elevated levels in adults. Serial fasting blood samples were collected annually between the 9th and 21st birthdays for assessment of TC, LDL-C, and HDL-C</td>
<td>( 9 ) and ( \sigma ) had similar patterns of change over the period of the study No significant differences were observed between ( \sigma ) and ( 9 ) for any of the lipid parameters over the course of the study. Tracking correlations for TC, LDL-C indicated &quot;good predictive value at ages 9-11 for risk of elevated concentrations at age 19-21.&quot; &quot;Tracking of HDL-C was less marked but the patterns were similar.</td>
<td>No diet, family, or demographic data included. No anthropometric data included.</td>
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Table 5c: Studies of CVD Risk Factors in Children: Hypertension

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<td>Berenson et al., 1996</td>
<td>A subset of the Bogalusa study sample was used along with a sample (n=401) of 5-17 year old Hispanic children from a different study of CVD risk factors, the Brooks County Study which took place in Texas during the years 1984-1985.</td>
<td>This report is a description of a study to describe differences in BP in three ethnic groups over time. BP values represent the mean of three readings from two observers. Anthropometric data were also collected at the time of each examination.</td>
<td>In the Bogalusa cohort, black♂ had higher BP than other groups. Hispanic ♀ had lower SBP than other groups.</td>
<td>The sample description from the Bogalusa study was not clearly described. For instance, it was not made clear what surveys the Bogalusa sample was drawn from, or whether the examinations were serial or occurred once and the trends discussed were secular trends rather than tracking within individuals. Presumably it was the former.</td>
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<td>Del Rosario et al., 1998</td>
<td>Subjects were 88 children 7 to 15 y (mean age 10.9 y; 52 blacks; 24 ♀, 28 ♀, 36 white 19 ♀, 17 ♀). All subjects had physician-verified history of essential hypertension in at least one parent and grandparent.</td>
<td>This study was designed to identify predictors of BP in normotensive youths with family history of essential hypertension. Examinations included anthropometrics, BP at rest, and before, during and after 3 laboratory stressors: postural change, forehead cold, and a video game. Ambulatory BP was monitored for 24 h during a follow-up exam approximately 2.5 after initial exam.</td>
<td>Height, weight, resting SBP were all significantly increased at the follow-up. DBP was significantly decreased. At follow-up ambulatory daytime SBP was significantly greater in boys than girls and the decrease in DBP was also significantly greater in boys than girls. No difference was noted in nighttime SBP. Nighttime SBP in girls was significantly less than boys. BMI was significantly associated with daytime SBP. Body surface area was associated with both daytime and nighttime SBP. No racial differences were reported.</td>
<td>This was a descriptive study that contained no data on diet or demographics.</td>
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<td>Elkabasany et al., 1998</td>
<td>2,530 subjects from the Bogalusa study sample had BP measured as and child and as a young adult.</td>
<td>The objective of this study was to determine the predictability of adult DBP from childhood measures. The particular focus was on the utility of the fourth Korotkoff phase (K4; the point of muffling of sound) versus the fifth phase (K5; the disappearance of sound) as predictors of DBP. 6 BP readings were taking at each screening with K1, K4, and K5 recorded.</td>
<td>“During childhood, K4 is a more reliable measure of DBP than K5. K4 DBP measured in childhood is a better predictor of adult hypertension.”</td>
<td>This was a methodological study that provided little evidence with regard to hypertension and/or its correlates and risk of CVD.</td>
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<td>Dietary Intervention Study in Children (DISC) (Simons-Morton et al., 1997)</td>
<td>Subjects were participants in the DISC study, a &quot;randomized controlled trials to test the efficacy and safety of dietary intervention for lowering elevated LDL-C in pubescent children.&quot; Baseline data were available for 653 subjects (mean age 9.6 y, 46%♀)</td>
<td>Objective was to investigate the relationships between dietary nutrients and BP in children over a three-year period in subjects involved in a dietary intervention. Dietary intervention was individual, family, and group education designed to achieve dietary goals of 28% calories from fat, 8% calories from saturated fat, 9% from polyunsaturated fat, and 75 mg cholesterol/1000 kcal not to exceed 150 mg/d. 3 non-consecutive 24 h dietary recall (first at face-to-face interview, subsequent recalls over telephone) were collected at each time period. The three recall were averaged to represent intake at each time period. Micronutrients evaluated were calcium, magnesium, potassium, and cholesterol, macronutrients were fat, protein, and carbohydrates. Sodium use was not assessed.</td>
<td>SBP was inversely associated with calcium, magnesium, potassium, and protein, and positively associated with total fat and mono-unsaturated fat. DBP was inversely related to calcium, magnesium, potassium, protein, carbohydrates and fiber. DBP was positively associated with poly- and mono-unsaturated fats. “Results from this sample of children with elevated LDL-C indicate that dietary calcium, fiber, and fat may be important determinants of BP level in children.” No significant differences in BP changes between intervention and non-intervention groups. nor any changes in BP relative to the changes of intake of nutrients over time.</td>
<td>Racial or demographic characteristics of the study sample were not provided.</td>
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<td>Muscatine Study (Lauer et al., 1993)</td>
<td>see previous discussions of the Muscatine Study Subjects (n=2,446 first examined at ages 7-18 and reexamined between 20-30 y.</td>
<td>The objective was to describe the risk for high BP in young adult life based on observations made in childhood. Measures included BP (K1, K4 for children; K1 and K5 for adults) height, weight, TSF,</td>
<td>&quot;Adult ponderosity was related to childhood ponderosity, and those who were most obese as adults showed the greatest increase in weight from their childhood years.&quot; Childhood SBP at all time points was significantly associated with adult SBP as was the change in BMI. &quot;These observations suggest that strategies to prevent the acquisition of excess ponderosity during childhood may be more useful in preventing adult hypertension.&quot;</td>
<td>See comments from previous reviews of the Muscatine study above.</td>
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<td>Pathobiological Determinants of Atherosclerosis in Youth (PDAY) (McGill et al., 1998)</td>
<td>see previous descriptions of the PDAY cohort.</td>
<td>see previous descriptions of the PDAY study Hypertension was diagnosed based on the ratio of intimal thickness to outer diameter of the small renal arteries to predict mean arterial BP and was defined as mean arterial BP $\geq 110$ mmHg.</td>
<td>“Hypertension had little or no effect on fatty streaks.” Hypertension was associated with more extensive raised lesions in the abdominal aortas and right coronary arteries of blacks $&gt;20$ y of age and in the right coronary arteries of whites $&gt;25$ y.” “Hypertension was associated with larger diameters of the right coronary arteries and left anterior descending coronary arteries and with larger cross sectional intimal and medial areas of the left anterior ascending arteries.” “Hypertension augments atherosclerosis in both men and women primarily by accelerating the conversion of fatty streaks to raised lesions beginning in the third decade of life, and the effect of hypertension increases with age.”</td>
<td>See previous discussions of the PDAY study.</td>
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<td>Sodium-Potassium Blood Pressure Trial in Children (Sinaiko et al., 1994)</td>
<td>From an initial BP screening of 19,452 subjects with SBP &gt; 70th percentile of sex-age-specific distribution had second BP measurement. After 2nd measure all black, white, and Hispanic children in the upper 15th % of BP distribution (SBP &gt; 109 mmHg for σ, and 108 mmHg for ψ) were invited to participate (n=3,223) of those 243 (8%) agreed to participate in the 4 y trial and were referred to as the high-normal group. An additional 40 students were randomly selected from the lowest 10% of BP to serve as the control group. No significant differences were noted for BP, anthropometrics, race, sex, or ethnicity between those enrolled and children in the respective highest 15th and lowest 10th percentile groups who choose not to participate.</td>
<td>Objective was to compare serum calcium levels, dietary calcium intake and calcium excretion in 11-14 y old students with high and low-normal BP. Non-fasted blood samples were collected in the afternoon at school. Calcium intake was determined in the high-normal group only and was based on food diaries from three consecutive days (2 weekdays, 1 weekend). 24 hour urine was collected during the same week as the diet diaries.</td>
<td>Weight and BMI were significantly greater in the high-normal versus controls. Significant differences were also noted for various fractions of calcium in blood with controls having &gt; serum ultrafilterable, true ionized, ionized normalized for pH and complexed calcium than controls. Bound serum calcium was &gt; in the high normal group than in controls. The controls excreted significantly more calcium than the high normal group. No differences were observed for sodium, potassium, or chloride excretion. No intake differences were noted. &quot;The results suggest that calcium metabolism may differ between individuals with low and high-normal BP during the first two decades of life and prior to the onset of essential hypertension.&quot;</td>
<td>Selection bias has to be considered in light of the low enrollment. No data on parental attitudes, SES, education etc. were collected that might have shed light on this issue. In light of the extent of unwillingness of those in the high normal group to participate it is not clear how the control group was selected. Did all 40 identified agree to participate or did the investigators keep calling until they convinced 40 subjects to participate?</td>
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| Tecumseh, MI (Kneisley et al., 1990) | 576 subjects (271♂ mean age 32 y) were evaluated. Data were available for 368 mothers (mean age at exam 30y) and 351 fathers (mean age at exam 32.8 y) of study subjects. | Childhood BP data were 3 taken at 2 exams one at about 5.3 y and one at about 8 y. Subjects with data from both time (n=423) had values and ages averaged. 223 subjects had only one reading. Similar pattern of exams occurred as adults 429 subjects had readings twice and 144 subjects had only one exam. | ♀: Significant correlations were observed between SBP at 32 and SBP at age 7, age 22 and paternal SBP, DBP, heart rate, weight and subscapular skinfold (SSF) at 22. ♂: SBP at age 32 was correlated with SBP and SSF at 7, 22, and in both parents, DBP and weight at age 7, 22, and in mother, and heart rate at age 22. Using a step-wise discriminate analysis the combination of weight at age 22, SBP at 22 and father’s DBP correctly predicted BP at 32 in 89% of the sample.
A gradient of risk was found when current BP was assessed with respect to previous BP classification (upper 20%) family background, and overweight. The lowest risk was associated with high childhood BP (19% compared with 12% in the overall population). The highest risk was in those with high BP and overweight at 22y with a family history. | No diet, demographic data on subjects or follow-up data on parents. |
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<th>Study (Reference)</th>
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<th>Results and Authors’ Conclusions</th>
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<tr>
<td>Gidding et al., 1995</td>
<td>See previous descriptions of the Bogalusa Heart Study 2 cohorts: #1: Baseline (1973) at 7-9 y of age and reexamined in 1981 (n=417) #2: Baseline 1984 and reexamined in 1992 (n=417)</td>
<td>Study designed to determine whether the secular trend towards increased weight gain tracked over a period of 11 years and to determine whether an association exists between this trend and risk factors for CVD. Measurements at exam: age, gender, race, height, weight, BP, lipoproteins. Cohorts were compared.</td>
<td>A significant increase in ponderosity was observed in all groups (not statistically significant in white ♂ that was associated with changes in lipid profiles. Other significant changes included increases in LDL-C in black ♂, TG in black and white ♂ and white ♀, and decreases in HDL-C in black ♂ and ♀ of both races. TC was changed significantly only in white ♀ (significantly increased in cohort #2). “There is a secular trend toward increased ponderosity in children examined in the Bogalusa Heart Study. This trend is associated with worsening cardiovascular risk, particularly with regard to lipoproteins.”</td>
<td>See previous comments on the Bogalusa Heart Study</td>
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<td>Srinivasan et al., 1996</td>
<td>See previous descriptions of the Bogalusa Heart Study</td>
<td>Two objectives 1) determine the risk for overweight adolescents to remain overweight as young adults, 2) to assess the association of multiple cardiovascular risk factors with adult overweight of adolescent onset. Subjects were divided into two categories; adolescent onset adult overweight (began and remained above the 75th percentile; n=110) or lean (those who began and remained between the 25th and 50th percentiles; n=81) based on the BMI percentile distribution of the Bogalusa population. See previous descriptions of Bogalusa Heart Study for further methodological details.</td>
<td>The overweight cohort had significantly higher values for skinfolds, SBP, DBP, TC, TG, LDL-C, insulin, and glucose, and lower levels of HDL-C than the lean group. Parents of the overweight group had significantly higher incidence of diabetes mellitus, and hypertension. A significantly higher percentage of overweight subjects had adverse levels (i.e., beyond NCEP standards) for LDL-C, TG, and HDL-C. The overweight group had a significantly higher risk for clustering of adverse risk factors (≥75th percentile levels of 2 or 3 risk factors) as adults.</td>
<td>See previous comments on the Bogalusa Heart Study It was not made clear why the cohort was limited to only 783 when these types of data were available from a larger number of subjects who participated in both the follow-up survey and at least one other baseline survey. Rather than using the conventional criteria of BMI &gt; 95th percentile of the general population to define obesity, the authors used the &gt;75th percentile of their resident study population. No justification was provided for this approach. Of 783 subjects only 191 were categorized according to study criteria. Consequently 592 subjects fell into either the very lean category, i.e., BMI &lt; 25th percentile or between the 50th and 75th percentile. No discussion or analysis of these subjects were included or explanation for why they didn’t use distributions, e.g., quartiles, to determine tracking and allow for use of the whole cohort.</td>
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<td>Williams et al., 1992</td>
<td>See previous descriptions of the Bogalusa Heart Study</td>
<td>Goal was to determine the level of body fatness, independent of fat patterning, associated with significant risk for elevated BP, TC and serum lipoprotein ratios. Total body and regional fat were estimated from triceps (TSF) and subscapular skinfold (SSF). Body density was estimated from age and the sum of TSF and SSF and was used to estimate total percent body fat. To establish associations with risk factors subjects were categorized according to level of percent body fat, $\sigma$: &lt;10% (n=217), 10-14.9% (n=575), 15 to 19.9% (n=436), 20-24.9% (n=192) and &gt;25% (n=247). $\varphi$: &lt; 20% (n=547), 20-24.9% (n=493). 25-29.9% (n=313), 30-34.9% (n=192), &gt; 35% (n=108). BP measured and blood lipids were collected to determine extent of risk. The uppermost quintile of the Bogalusa sample was chosen to define elevated CVD risk factors.</td>
<td>&quot;Significant over-representation (&gt;20%) of the uppermost quintile for CVD risk factors was evident at or above 25% fat in males (32.2% to 37.3% in the upper quintile) and at or above 30% fat in females (26.6 -45.5% in upper quintiles) even after adjusting for age, race, fasting status, and trunkal fat patterns.&quot;</td>
<td>See previous comments on the Bogalusa Heart Study</td>
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<td>Study (Reference)</td>
<td>Subject Number and Description</td>
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<td>Minneapolis Children's Blood Pressure Study</td>
<td>Study began 1977-1978 by screening BP in 10,423 children in grades 1-3. A follow-up cohort was selected based on all children from the top and bottom 5% of SBP distribution, 50% of remaining black children and 1 of 9 of remaining white children, and all others. Written consent was obtained for a total of 1207 (45%) of the potential pool of 2641. The 1207 were examined twice yearly through high school, annually during high school, two years after high school graduation (n=817; 67% of the 1207) and five years later during period of 1993 to 1995 (n=679; mean age 23.6 y).</td>
<td>This report is a description of a study designed to address the effect of body size and change in body size during childhood and adolescence on the cardiovascular risk factors of fasting insulin, lipids and SBP in young adulthood. BP and anthropometric assessments (for calculation of BMI) were conducted at all examinations. Blood samples were collected only in the last examination for analysis of insulin, TC, HDL-C, TG, and LDL-C</td>
<td>Mean age at the beginning of the study for the 679 subjects was 7.7 y and 23.6 y at final follow-up. &quot;Initial childhood weight, BMI and height were significantly correlated with young adult weight, BMI and height and with fasting insulin, lipids [TG, HDL-C], and SBP, The increases in weight and BMI but not height during childhood were significantly related to the young adult levels of insulin, TG, HDL-C, and SBP.&quot; No significant associations were observed between body composition and either TC or LDL-C. &quot;...weight gain in excess of normal growth during childhood is a determinant of adult cardiovascular risk. &quot;...weight gain rather than the childhood weight at 7.7 y of age is significantly related to young adult risk factors suggests that a reduction in weight gain could reduce subsequent levels of cardiovascular risk.&quot;</td>
<td>No diet, demographic or family history data collected. No discussion of the potential selection bias in the study population related to large drop-out rate (55%) of the original sample selected (n=2641) compared with those who agreed to participate (n=1207) and the number who ultimately participated in the last follow-up examination (n=679 or 56% of the 1207 or 25% of the original 2641 eligible subjects) No discussion of attrition rates between original examination and last follow-up or characteristics of participants with those who dropped out.</td>
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<td>Study Description</td>
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<td>Muscatine Ponderosity Study (Burns et al., 1989)</td>
<td>See previous descriptions of the Muscatine protocol Out of a total of 1,783 subjects who participated in three surveys conducted in the Muscatine school system, a total of 284 subjects between ages of 5-14 y at time of first evaluation and their families were divided into five groups: lean (L; students in the 1st quintile of weight on all three surveys n=72), random (RG; a random sample of all eligible students; n=70), lean gain (LG; n= 50), heavy gain (HG; gain of at least 2 quintiles of relative weight from the first or second survey to the second or third survey, n=20), and heavy group (H; n=70); subjects in the 5th quintile of weight on all three surveys.</td>
<td>Designed to evaluate the relation between ponderosity in children and coronary risk factor levels in these children and their family members and the genetic contribution to familial clustering of levels of ponderosity. In addition to the students, family members examined included parents, siblings, a related aunt or uncle, and a first cousin.</td>
<td>Levels of HDL-C, apolipoproteins A-I and B, and SBP in heavy group are &quot;consistent with increased coronary risk. This same association exists among the relatives with excess ponderosity. Levels of BMI in the mothers, fathers, and siblings cluster with the levels in the probands, and genetic differences among person explain 36-52% of the variability in BMI across the range of ponderosity represented by the probands and their relatives.&quot; HG groups was &gt; LG for TC, &gt; L, R, LG for LDL-C, &gt; L for SBP H group was &lt; L, R, LG for HDL-C, &gt; LG for TG, &gt; L, R, LG for SBP. For BMI: Mothers of H &gt; L, R, LG, fathers of H &gt; L, R, siblings of H &gt; L, R, LG, and aunts and uncles of H &gt; L, R Overweight parents and siblings had &gt; SBP, DBP, and TG and &lt; HDL-C than relatives of non-overweight subjects TC of only fathers of overweight subjects were &gt; and only mothers and siblings had &gt; LDL-C than those of non-overweight subjects &quot;While the contribution form genes is strong, these data suggest that the contribution from environmental factors is equally as important.&quot;</td>
<td>No data or analysis of diet or other potential environmental influences were included in this report.</td>
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### Table 5e: Childhood Interventions

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<th>Study (Reference)</th>
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<th>Methods Outcome Variables</th>
<th>Results and Authors’ Conclusions</th>
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<td><strong>DISC Collaborative Research Group:</strong> The Writing Group (1995)</td>
<td>Based on a power analysis designed to determine the n to detect a difference of 0.14 mmol/L (5.4 mg/dL) in LDL-C, 0.8 cm in height, and 3.5 μg/L in serum ferritin, a sample size of 600 was required. Age eligibility for 6 was 7 to 10 m to 10 y 1 m, for 11 years 7 m to 10 y 10 m Subjects were recruited by mass mailings to HMO and pediatric practices and from public and private elementary schools. After a two-phase screening process 663 eligible subjects were identified based on the average of two screening LDL-C values being ≥80th and &lt; 95th percentiles for age and sex.</td>
<td>The objective of the DISC study is to “assess the efficacy and safety of lowering dietary intake of total fat saturated fat, and cholesterol to decrease LDL-C levels in children.” Eligible subjects were randomly assigned to treatment groups; intervention was a series of family, group, and individual teaching sessions intended to instruct children and their families to follow a diet containing 28% calories from fat (&lt;38% as saturated fat, up to 9% as PUFA, 11% as mono-unsaturated fat) and dietary cholesterol &lt;75 mg/1000kcal (&lt;150 mg/d). Measurements included: LDL-C, TC, TG, HDL-C, dietary assessments (3 non-consecutive 24 hr recall within 2 weeks of clinic visits), skinfold measurements, body circumferences, and BP at baseline, 1 year and 3 years (end of trial). Blood micronutrients, albumin, and psychological assessments were made at baseline and year 3.</td>
<td>At 3 years, dietary total fat, saturated fat, and cholesterol levels decreased significantly in the intervention group compared with the controls. LDL-C decreased in both groups. (A finding consistent the age related decreases in LDL-C reported in the Bogalusa Heart Study). Adjusting for baseline level and sex and imputing values for missing data, the mean difference between the groups was -0.08 mmol/L (3.23 mg/dL) which was significant (p=0.02). No differences reported for height or serum ferritin. “The dietary intervention achieved modest lowering of LDL-C levels over 3 years while maintaining adequate growth, iron stores, nutritional adequacy, and psychological well-being during the critical growth period of adolescence.”</td>
<td>The study description implies that all eligible children participated. Consequently out of 44,000 children initially screened only 663 were eligible and all agreed to participate. Control group parents were informed that child’s blood cholesterol was high and the parents received the American Heart Association publication, “Dietary Guidelines for Americans” and “How to Make Your Heart Last a Lifetime”. Consequently the trial compared the intensity of similar education programs. This was born out by the results which showed similar trends in the desired direction in both groups for the main outcomes, LDL-C and dietary fats... The study might have benefited from an age, sex-matched randomly selected control group who received no information about diet and health. Significant differences were reported for baseline characteristics: intervention group had lower % calories from PUFA, higher intakes of vitamin B6 zinc, higher proportion of household income &lt; $20,000. The DISC group suggested that in the “context of multiple comparisons, it appears randomization yielded comparable treatment groups...”</td>
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<td>9 155</td>
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<td>total 334</td>
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<td>white 289</td>
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<td>black 25</td>
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<td>Kwiterovich et al., 1997</td>
<td>See DISC discussion above</td>
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<td>Obarzanek et al., 1997</td>
<td>See DISC discussion above</td>
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<td>Edmundson et al., 1996</td>
<td>Subjects were students from 96 elementary schools California, Louisiana, Minnesota, and Texas. 7,795 subjects (mean age 8.75 y) began the study in third grade.</td>
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<td>Jacobson et al., 1999</td>
<td>Subjects were 138 children (74♂, 64♀; 84% Caucasian) between the ages of 2 and 15 y referred to three centers in the N.Y. metropolitan area for treatment of hyperlipidemia (serum cholesterol &gt;95th percentile for age). For inclusion in the final data analyses, subjects had to have participated in at least 3 clinical visits over the 3-y intervention.</td>
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<td>Tershakovec et al., 1998</td>
<td>3652 children screened for TC, 997 met the study criteria for elevated TC (TC greater than 176 mg/dL, 75th percentile). 458 agreed to follow-up screening (LDL-C) 271 met LDL-C criteria (LDL-C 107 to 164 mg/dL for $\sigma$, 112 to 164 mg/dL for $\gamma$) and were randomized to three groups; 2 interventions, and an at-risk control group. An additional 81 children served as a “not-at-risk” control group.</td>
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CHAPTER 6. ADULT ONSET NON-INSULIN-DEPENDENT DIABETES MELLITUS (NIDDM)

A. BACKGROUND

Non-insulin-dependent diabetes mellitus (NIDDM) has been defined by the National Diabetes Data Group (National Diabetes Data Group, 1979) and the World Health Organization (WHO) (World Health Organization, 1994) as diabetes with resistance to ketoacidosis in the absence of exogenous insulin. NIDDM is a generic term covering a number of diseases that share many overlapping sets of symptoms of disturbed glucose homeostasis. Because of the heterogeneity in etiology, care should be exercised to not treat NIDDM as if it were a single entity. However, the vast majority of individuals with NIDDM do not require long-term administration of exogenous insulin for the preservation of life (Glaser & Jones, 1996). Most patients with adult-onset NIDDM have insulin resistance (i.e., the unresponsiveness to insulin) and pancreatic β-cell dysfunction, along with impaired glucose tolerance (Knowler et al., 1995). While recognizing that many variants and subtypes of NIDDM have been identified (e.g., NIDDM in childhood, maturity-onset diabetes of youth) and the fact that distinguishing between IDDM and NIDDM is often clinically challenging (Glaser & Jones, 1996), for the purposes of simplification the focus of this review will be on adult-onset NIDDM and will use the terms type II diabetes and NIDDM interchangeably.

NIDDM accounts for 90% of cases of diabetes (Feuerstein & Weinstock, 1997). There are marked geographic and ethnic differences in prevalence. Increased prevalence is found in Native Americans, African-Americans, Hispanics, Asian and Pacific Island Americans and females are more frequently affected than males (Feuerstein & Weinstock, 1997; Rosenbloom et al., 1998). The prevalence of early onset NIDDM appears to be on the increase in Native American and African-American youth (Rosenbloom et al., 1998).1

The development of adult-onset NIDDM has been divided into stages (Knowler et al., 1995). These stages may occur in overlapping time frames and in any individual NIDDM in individuals may progress through some or all of them (Knowler et al., 1995; Warram et al., 1997).

- Insulin resistance: Disorders of insulin metabolism, insulin signaling, glucose transport, glucose metabolism, energy metabolism or a variety of other metabolic disorders that generally manifest as a decreased responsiveness to insulin (Knowler et al., 1995). The genetic basis of insulin resistance is known in only a minority of the cases.

- Impaired glucose tolerance (IGT): Defined as blood glucose levels after ingestion of glucose that remain elevated above normal levels but below those levels necessary for a diagnosis of diabetes. This IGT is accompanied by insulin resistance and hyperinsulinemia.

- Diabetes without complications: May be defined when increased insulin secretion is no longer sufficient to compensate for the insulin resistance, and the hyperglycemia worsens to diabetes without complications. NIDDM often remains undiagnosed at this stage. The transition through the first three stages in any individual may take several decades.

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1 Recent studies suggest that early-onset classic NIDDM is the most common form in children and adolescents (Glaser, 1997). The noted increased prevalence in Native American and African-American youth refers to early-onset classic NIDDM.
Diabetes with vascular or neurological complications (Knowler et al., 1995). The complications of NIDDM include accelerated coronary artery and peripheral macrovascular disease, microvascular complications, nephropathy, retinopathy, and neuropathy (Feuerstein & Weinstock, 1997; Warram et al., 1997).

Improved control of blood glucose levels decreases the rate of progression of the complications (Feuerstein & Weinstock, 1997). The complete pathophysiology of NIDDM is complex, incompletely understood, and beyond the scope of this review.

B. BIOMARKERS AND RISK FACTORS IN ADULTS

IGT, which represents a state of balance between insulin resistance and compensatory insulin secretion, is probably the most reliable biomarker for NIDDM (Bennett, 1997). Others suggest plasma glucose levels are perhaps the best predictor of subsequent NIDDM (Ferrannini & Camastra, 1998). However, any subclinical feature of the early stages of NIDDM development such as hyperglycemia, elevated glycohemoglobin levels, IGT, insulin resistance, or hyperinsulinemia may be considered to be a biomarker for the disease (Ferrannini & Camastra, 1998; Knowler et al., 1995). Known risk factors of NIDDM also include obesity, especially central (or android) obesity; physical inactivity; and a high-fat diet (Knowler et al., 1995). Measures of obesity (BMI), central obesity (waist-hip ratio), and duration of obesity are all independent risk factors for NIDDM (Ferrannini & Camastra, 1998).

Individuals with close relatives with NIDDM, women with a history of gestational diabetes, and members of geographic or ethnic populations with a history of high prevalence of NIDDM represent high-risk groups as well (Bennett, 1997). However, there is a danger in discussing a broad-based disease of heterogeneous etiology as if it were a single entity. Adult-onset NIDDM may have a different set of risk factors and a different set of outcomes for Native Americans than for populations of Caucasian or Asian descent. However, the genetic contribution is unmistakable in some populations. Monozygotic twins have a concordance of 70-80% compared with the 10-20% concordance in dizygotic twins; the lifetime risk of developing NIDDM is 40% for offspring of a diabetic parent compared to the 3% prevalence world-wide (Groop & Tuomi, 1997).

C. DO ADULT BIOMARKERS APPEAR IN CHILDREN? DO THEY TRACK?

Because NIDDM may take several decades to progress through the stages of development, markers such as hyperglycemia, insulin resistance, hyperinsulinemia, and central obesity may appear during youth. However, even if these markers or other risk factors are appreciated in childhood or adolescence, it is difficult to distinguish them as early indications of adult-onset NIDDM from one of the early-onset variants that are prevalent, especially in minority children and adolescents (e.g. early-onset classic NIDDM, maturity onset diabetes of youth (MODY), insulin resistance syndromes, etc.) (Glaser, 1997).

Caprio et al. (1995) have shown that obese adolescent girls have evidence of hyperglycemia, hyperinsulinemia, and insulin resistance that is not apparent in nonobese control groups. Moreover, they found a strong correlation between visceral abdominal fat, hyperinsulinemia, and insulin resistance. This is evidence that the abnormalities associated with NIDDM are expressed early in the natural history of obesity.
Hong et al. (1998) found a significant familial correlation between abdominal visceral fat and insulin resistance, even after adjusting for total fat mass. Thus, the sons and daughters of parents with increased abdominal fat and/or insulin resistance have an increased likelihood of exhibiting those traits as well. Moreover, abdominal visceral fat and insulin resistance were shown to share common genetic influences; that is, they appear to be the outcome of the same genetic influences.

Two separate cohorts from the Bogalusa Heart Study compared offspring of families with a history of diabetes to matched control groups (Berenson et al., 1995, 1996; Srinivasan et al., 1998). Numerous indices of glucose homeostasis were significantly elevated in the offspring of diabetic families, including basal glucose levels, insulin resistance index, and insulin levels. (Srinivasan et al., 1998). Female offspring of diabetic families were heavier and had thicker skinfolds, more abdominal fat and higher BMI (Berenson et al., 1995, 1996). There were several significant racial differences, including lower measures of abdominal fat, glucose response, and insulin secretion in blacks regardless of parental diabetes status. Both studies demonstrate that is possible to identify metabolic abnormalities in childhood and adolescence that are risk factors for adult-onset NIDDM.

Other observations may provide clues that NIDDM begins in childhood before clinical manifestations are apparent. Low birth weight is a risk factor for NIDDM. Crowther et al. (1998) found an inverse correlation between low birth weight and hyperinsulinemia and between birth weight and glucose levels in black South African children. Children born with low birth weight but who had high weights at 7 years of age had a higher index of obesity and higher insulin levels which may make them susceptible to NIDDM later in life (Crowther et al., 1998). Lower ponderal index at birth (birth weight/birth length$^3$) was associated with insulin resistance at age 50 yr and NIDDM at age 60 yr in a study of Swedish men (Lithell et al., 1996). Thus, reduced fetal growth is associated with an increased risk of diabetes, which appears to depend on obesity in adult life (Lithell et al., 1996). Two competing hypotheses (one focusing on environmental exposures during intrauterine development [the Barker hypothesis] and the other on genetic causes) have been advanced to explain these effects (Morris, 1998). In some populations there is evidence that NIDDM is transmitted in utero from mothers with gestational diabetes (Moses et al., 1997). If the disease is indeed acquired this early, it has implications for tracking of the biomarkers and suggests the possibility of early detection.

Some support for tracking was provided by analysis of the data from the Bogalusa Heart Study (Bao et al., 1996b). A longitudinal study was constructed out of two cross-sectional studies conducted eight years apart. Insulin levels appeared to track; those individuals in the lowest and highest quartiles tended to remain in those quartiles over the course of the study. Individuals in the highest insulin level quartile also had elevated levels of NIDDM risk factors including, body mass index (BMI), triglycerides, VLDL, LDL cholesterol, glucose levels, blood pressure, and a higher prevalence of parental diabetes. NIDDM risk factors appear to track from childhood through young adulthood. Using parental history as a surrogate measure of future risk, the risk factors may track into manifest adult-onset NIDDM (Bao et al., 1996b).

D. DIETARY LINKS TO BIOMARKERS: DO THEY TRACK?

Because NIDDM and cardiovascular disease share so many risk factors in common, some dietary antecedents of NIDDM may also be the same as those for cardiovascular disease. About 60-80% of adult NIDDM patients are obese (Group & Tuomi, 1997). Obesity, in particular central or abdominal obesity, and physical inactivity have been shown to be independent risk factors for NIDDM biomarkers such as hyperinsulinemia and insulin resistance as well as for NIDDM itself. These are robust correlations, supported by the evidence from many independent studies in adults (Bao et al., 1996a; Berenson et al., 1996; Caprio et al., 1995; Ferrannini &
Camasta, 1998; Feuerstein & Weinstock, 1997; Hong et al., 1998; National Institutes of Health [NIH], 1997). In adults, evidence exists to support a linkage between high intake of dietary fat and hyperinsulinemia, insulin resistance, and diabetes (Knowler et al., 1995; Marshall et al., 1991, 1994; Prins, 1997; Stern, 1991). Two recently published prospective, longitudinal studies on adult subjects link the intake of increased amounts of dietary fiber, especially cereal fiber, and decreased dietary glycemic index (a qualitative indicator of the ability of carbohydrate to raise blood glucose level) with decreased risk of NIDDM (Salmerón et al., 1997a, b). In adults, decreased dietary energy intake, decreased fat intake, weight loss, loss of abdominal visceral fat, increased fiber intake, and increased physical activity have all been shown to prevent or delay insulin resistance, hyperinsulinemia, IGT, and NIDDM (Feuerstein & Weinstock, 1997; NIH, 1997).

Although no studies were found that directly linked dietary intake in children to adult-onset NIDDM, an indirect measure of this potential association may be found in the link between the growing incidence of obesity in children and the increased incidence of non-MODY NIDDM in African American and Native-American children (Glaser & Jones, 1996; Rosenbloom et al., 1998). A review of the prevalence and factors associated with the tracking of obesity may be found in Chapter 3.

E. INTERVENTIONS

The extensive evidence for the linkage between obesity and physical activity and NIDDM has been well recognized. In 1986, the National Institute of Health Consensus Development Conference on Diet and Exercise in NIDDM addressed several questions in the area including: the optimum dietary prescription, benefits and risks of exercise, and the evidence for a preventive effect (NIH, 1997). The Consensus Development Conference also raised new questions and suggested areas for future research. The research findings published subsequent to that conference were recently reviewed (Feuerstein & Weinstock, 1997).

The goals of a diet and exercise treatment program are to enhance control of glucose levels, decrease insulin resistance, and reduce the acceleration of macrovascular complications. In adults, the short-term benefits of such intervention programs have been well documented, however, long-term compliance has been very difficult to achieve. Poor long-term success of diet programs has led some physicians to become more interested in pharmacologic interventions (Feuerstein & Weinstock, 1997; Knowler et al., 1995). Others view this as a rapidly evolving field in which optimum programs have not yet been developed.

The study by (Uusitupa, 1996) is an example of an evaluation of the efficacy of a dietary and exercise intervention on newly diagnosed NIDDM adult patients. After one year of dietary restrictions (aimed at weight loss and reduced dietary intake of saturated fat) and increased physical activity, the subjects had moderately increased glycemic control, lower serum lipid levels, and increased serum HDL cholesterol levels. However, in a follow-up study on the same subjects conducted one year after the intervention was halted, significant deterioration was found in weight, glycemic control, serum lipids, and blood pressure.

The poor long-term success of diet programs for the treatment of adult-onset NIDDM and the knowledge that NIDDM can, in part, be preventable has led to efforts to prevent or delay NIDDM through diet and exercise programs aimed at children (Glaser, 1997; Knowler et al., 1995). Intervention in childhood and adolescence offers several benefits: interventions at school offer a "captive audience" eager to learn new ideas; a controlled environment wherein both dietary intake and physical activity can be altered; the opportunity to alter dietary and activity patterns at a time when the patterns are being established; and the potential long-term consequences of decreased risk factors that track into adulthood (Macaulay et al., 1997). As reviewed below, many such
intervention programs have been attempted with mixed success (Cook & Hurley, 1998; Feuerstein & Weinstock, 1997; Glaser, 1997; Holcomb et al., 1998; Macaulay et al., 1997; Teufel & Ritenbaugh, 1998; Trevino et al., 1998).

The Bienestar Health Program was designed to decrease body fat and/or dietary fat intake and increase vegetable and fruit intake, health knowledge, self-efficacy, and physical activity in fourth grade Mexican-American children (Trevino et al., 1998). The program includes nine months of comprehensive instructional program for parents, teachers, school cafeteria staff, and after-school caregivers, and monitors dietary intake as measured by three 24-hr dietary recalls. In a report on the preliminary results from the pilot study, Trevino et al. (1998) noted significant improvement in dietary fat servings, percent fat total energy, dietary fruit and vegetable servings, and diabetes health knowledge; however, there was no change in percent body fat.

The Kahnawake Schools Diabetes Prevention Project is a 3-year community-based prevention program for NIDDM targeting 6-12 yr-old Native children in Canada (Macaulay et al., 1997). The long-term goal is to decrease NIDDM, while short-term goals are to reduce prevalence of obesity, high-calorie/high-fat diets, and physical inactivity. Although the lack of controls impedes interpretation of the data, the baseline data reported show that between 9 and 10 years of age there are increased weight, height, BMI, and skinfold thicknesses, decreased fitness, and increased television watching. The results of the intervention are not yet reported.

Holcomb et al. (1998) described the Jump Into Action school-based NIDDM prevention program designed to encourage low-fat diet and increased exercise for fifth-grade, predominantly Mexican-American children. Significant improvements in students' knowledge, dietary fat intake (assessed by a limited recall questionnaire) and self-reported exercise levels were reported after six weeks of instruction and maintained four weeks later on follow-up exam. The lack of controls and lack of randomization of selection of subjects, possible response bias in testing, and incomplete sampling limit the interpretation of the results from this study.

The Quest program, which has targeted Native American (Pima) children in grades K-2, has four components: biochemical and anthropometric assessments, classroom instruction about diabetes, increased physical activity at school, and a structured school breakfast and lunch program (Cook & Hurley, 1998). These investigators described the challenges of designing such a program, including the difficulties in attaining compliance in an typically rebellious, adolescent population, and the difficulty in balancing federally mandated dietary guidelines for Nu-Meals programs and the special needs of the target population. No results were included in the preliminary report (Cook & Hurley, 1998).

The Zuni Diabetes Prevention Program was a community-based program that involved high-school-age youths, with the goal of reducing the prevalence of diabetes risk factors via diabetes education, a school-based wellness center, supportive social networks, and modification of the food supply available to teens (Teufel & Ritenbaugh, 1998). Five primary risk factors were targeted: obesity and pattern of fat distribution, insulin resistance, low physical activity, high consumption of sugared beverages, and low consumption of high-fiber foods such as fruits and vegetables. In their analysis of the midpoint results from this four-year project (Teufel & Ritenbaugh, 1998) reported a significant reduction in soft drink consumption and an increase in glucose/insulin ratios, suggesting a decline in hyperinsulinemia.
Table 4a: Major Studies of NIDDM Risk Factors in Children

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<tr>
<th>Study (Reference)</th>
<th>Subject Number and Description</th>
<th>Methods Outcome Variables</th>
<th>Results and Authors’ Conclusions</th>
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<td>Birth-to-Ten Study Group: South Africa (Crowther et al., 1998)</td>
<td>A longitudinal cohort was selected from the Birth to Ten study group. 152 seven-yr-old children (79♂ and 73♀) of black South African ethnicity.</td>
<td>Birth weight, height at 1 yr, height at 7 yr, BMI at 7 yr, subscapular and triceps skinfold at 1,2,4 and 5 yr and weight velocity between birth and 7 yr were included in the analysis. A 2 hr oral glucose tolerance test was performed; glucose and insulin levels were monitored. Insulin resistance was calculated.</td>
<td>Inverse correlations were found between birth weight and insulin secreted and between birth weight and glucose levels. Children born with low birth weights but who had high weights at 7 yr had higher insulin levels and higher indices of obesity. There were positive correlations between weight velocity and BMI and weight velocity and insulin resistance. “Thus, low birth weight in conjunction with rapid childhood gains in weight, especially as subcutaneous fat, produces poor glucose tolerance in 7-year-old children and can make them susceptible to the development of Type II diabetes later in life.”</td>
<td>The incidence of diabetes was not measured. The relationships of these risk factors to subsequent manifestation of diabetes would solidify this link. Low birth weight and stunting have been associated with poor fetal and neonatal nutrition.</td>
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<td>Bogalusa Heart Study (Dao et al., 1996a)</td>
<td>Subjects were chosen from the Bogalusa Heart Study. 1606 individuals (39% black, aged 5-23 yr for the first survey) were selected because they participated in both the baseline and follow up surveys. 739 were young adults (age 20-31 yr) at the time of the follow up survey.</td>
<td>Subjects were surveyed at onset and after an 8 yr period. Only those subjects that participated in both surveys were selected for analysis in this report. Height, weight, BMI, blood pressure and parental history of cardiovascular disease (including diabetes) were obtained at entry. Serum cholesterol, VLDL, LDL, HDL, triglycerides, insulin and glucose were obtained.</td>
<td>The authors constructed a longitudinal study out of two cross-sectional surveys from the same cohort conducted 8 years apart. Subjects were stratified by age, race, and sex; regardless of race and sex, 5 - 9 yr-old subjects presented significant increases in insulin levels. Tracking was ascertained by identifying those individuals whose insulin levels were persistently in the highest or lowest quartile during both surveys. Tracking of insulin levels was statistically significant, with a correlation of 0.23 to 0.36, with a greater magnitude in older subjects. Individuals in the highest insulin level quartile also had elevated BMI, triglycerides, VLDL and LDL cholesterol levels, glucose, and blood pressure; lower HDL levels, and higher prevalence of parental history of diabetes. There was a significant clustering of risk factors (obesity, hypertension, and dyslipidemia) which was stronger in adults with persistent insulin elevation. In &quot;Elevated insulin levels persist from childhood through young adulthood, resulting in a clinically relevant adverse risk profile in young adults.&quot;</td>
<td>This study did not measure clinically manifest diabetes. The authors suggest parental history as a surrogate measure of future risk. Hyperinsulinemia itself is a risk factor for diabetes. The presence in children and young adults of multiple diabetes risk factors and parental diabetes along with evidence for tracking demonstrates the potential for early intervention.</td>
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<td>Bogalusa Heart Study (Bao et al., 1996b; Berenson et al., 1995)</td>
<td>White children (n=52, age 7-31, average 15.3 yr) from 13 families with a history of onset of diabetes mellitus after the age of 30 yr and 12 control families. 21♂ and 31♀. All subjects were a subgroup of the Bogalusa Heart Study.</td>
<td>Anthropometric measurements included weight, BMI, subcapular and triceps skinfolds, and waist-hip ratio. Basal measures included blood pressure, serum lipid profiles, glucose, insulin, free fatty acids, glucagon, and others. In addition, all subjects were administered a standard glucose tolerance test.</td>
<td>Female offspring from diabetic families were heavier and had thicker skinfolds, higher waist-hip ratios, and higher BMI. They also had higher fasting insulin levels, insulin-to-glucose ratio, and insulin-to-C-peptide ratio. Male offspring from diabetic families had similar, non-significant trends, and significantly elevated blood pressure as well. Both male and female offspring from diabetic families had higher levels of glucose during the tolerance test; females also showed higher levels of insulin. &quot;Although obesity is an important predictor of type II diabetes, obesity alone cannot explain all the underlying metabolic abnormalities, because about one-third of the case subjects in the current study would not be considered obese by our population standards.&quot; &quot;These observations suggest abnormalities consistent with diabetes mellitus are already present in children and young adults, and may be detected by a response to glucose load.&quot;</td>
<td>Although the study did not discriminate between IDDM and NIDDM, the higher prevalence of NIDDM should dominate the results. The results of this study, though statistically significant, are relatively subtle. This is essentially a cross-sectional study conducted in the midst of a longitudinal study and is not strong evidence of tracking.</td>
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<td>Caprio et al., 1995</td>
<td>14 obese adolescent girls (average age 13.2 yr), 16 nonobese adolescent girls (average age 12.5 yr) and 14 nonobese young women (average age 24 yr). The adolescent groups were matched for stage of pubertal development. The obese subjects had a BMI greater than 95th percentile, nonobese subjects had a BMI in the 50th percentile.</td>
<td>Insulin action was studied by a two-step euglycemic clamp in combination with labeled glucose and indirect calorimetry. Insulin secretion was studied by hyperglycemic clamp. Visceral and subcutaneous fat was measured by magnetic resonance imaging. Outcome variables included: lipid oxidation, glucose oxidation, plasma free fatty acids, total body glucose disposal, basal and stimulated plasma glucose, plasma insulin, and plasma C-peptide.</td>
<td>In obese girls, glucose disposal was impaired, the response of plasma free fatty acid levels to insulin was impaired, glucose and lipid oxidation responses to insulin were diminished, and fasting and glucose-stimulated insulin responses were greater than in nonobese adolescents. Visceral fat but not waist-hip ratio nor subcutaneous fat was highly correlated to basal insulin secretion, stimulated insulin secretion, and insulin resistance. &quot;Increased visceral fat, hyperinsulinemia, and insulin resistance (involving glucose and lipid metabolism) are closely linked abnormalities that are expressed early in the natural history of obesity. Adolescents with central adiposity should be targeted for weight reduction and health surveillance to reduce morbidity of adult obesity.&quot; These results are free from the complications of life-style conditions such as smoking, chronic alcohol consumption, and uncontrollable stress.</td>
<td>Many of the biomarkers/risk factors for adult-onset NIDDM are apparent in obese adolescents. This was not designed as a longitudinal, tracking study. A cluster of cardiovascular risk factors (central obesity, hypertriglyceridemia, hyperinsulinemia, and high blood pressure) related to insulin resistance syndrome found in childhood may be predictive of subsequent diabetes.</td>
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<td>Bogalusa Heart Study (Srinivasan et al., 1998)</td>
<td>Subjects were selected from participants in Bogalusa Heart Study. Offspring of one type 2 diabetic parent (n=53, 53% white, 48% ?) were compared to offspring of families with no history of diabetes (n=52, 60% white, 50% ?) matched by the age of the parents. Age of offspring ranged from 7 - 25 yr, average 15 yr, 81% were under the age of 18.</td>
<td>Anthropometric measures included weight, height, skinfold thickness (both triceps and subscapular) waist-hip circumference. Blood pressure, cholesterol profiles, triglycerides, free fatty acids, insulin, proinsulin, glyced hemoglobin, C-peptide, and other indexes of glucose homeostasis were measured, as well as a 1 hr glucose tolerance test. Results were stratified by race and sex, and is some cases adjusted for BMI and waist.</td>
<td>Body weight, BMI, and skinfold measures were higher only in white offspring of diabetics; abdominal fat as measured by waist circumference and waist-hip ratio were higher in offspring of diabetics of both races. Among the measures of glucose homeostasis, basal glucose, insulin, a measure of hepatic insulin extraction, insulin resistance index and glucose response after glucose challenge were higher in the offspring of diabetics from both races. Hepatic glucose extraction and glucose response remained significant after adjustment for BMI and were independently associated with parental diabetes. Some traits differed between races: waist-hip ratio, glucose response, and a measure of insulin secretion were lower and other measures elevated in blacks versus whites regardless of status of parental diabetes. “In summary, our study demonstrates that it is possible to identify metabolic abnormalities in early life among those at high risk to develop type 2 diabetes, and that black-white differences in factors governing glucose homeostasis occur in youth, regardless of parental history of disease. Since type 2 diabetes is a heterogeneous disorder, long-term follow up studies are needed to ascertain the relationships between the observed correlates of parental disease and development of diabetes later in life in the two racial groups.”</td>
<td>This study did not measure clinically manifest diabetes. Parental history is used as a surrogate measure of future risk. Hyperinsulinemia itself is a risk factor for diabetes. The presence in children and young adults of multiple diabetes risk factors and parental diabetes has practical implications for prevention or delay of onset of diabetes through control of obesity and increased physical activity early in life.</td>
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<td>HERITAGE Family Study (Hong et al., 1998)</td>
<td>98 nuclear families of Caucasian descent, each with biological parents and at least two biological children. 512 subjects in all.</td>
<td>Fasting plasma insulin levels and abdominal subcutaneous fat and total fat were obtained at baseline and after a 20-week standardized exercise training program. Only the baseline data are reported in this publication. Familial correlations and cross-trait correlations were ascertained by statistical analysis.</td>
<td>The maximal heritability for abdominal visceral fat was 42% before and 50% after adjustment for total fat mass; for insulin it was 21%. 29% of the familial influences on insulin were also common to abdominal visceral fat; 14% of the familial influences on abdominal visceral fat were shared by insulin. After adjustment for total fat mass, these influences both increased. &quot;Genes and/or familial nongenetic factors with pleiotropic effects seem to influence both abdominal visceral fat and plasma insulin levels to a certain degree.&quot;</td>
<td>These findings indirectly support the notion that abdominal visceral fat is an important independent correlate of insulin resistance. It is difficult to distinguish between genetic and environmental factors in intact nuclear families. The authors infer a predominantly genetic causality from the observed heritability patterns.</td>
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<td>Uppsala, Sweden (Lithell et al., 1996)</td>
<td>1333 white adult♂ born between 1920-1924 in Uppsala, Sweden and still residing in Uppsala between 1970-1973 and in 1980.</td>
<td>A 1 hr oral intravenous tolerance test during which glucose and insulin levels were measured, fasting triglyceride, HDL levels, and BMI were measured at age 50 yr (during 1970-1973) and again at age 60 yr (during 1980). The main outcome measures were intravenous glucose tolerance test at age 50 yr and NIDDM at age 60 yr. Birth weights, length, and ponderal index(birth weight/birth length³). were obtained from hospital records.</td>
<td>There was an inverse correlation between ponderal index at birth and fasting insulin levels and insulin levels during the intravenous glucose tolerance test at age 50 yr. When participants were stratified by BMI, this association was stronger for those in the highest tertile for BMI. Prevalence for diabetes was 12% in the lowest quintile of ponderal index at birth compared to 4% in the lower 4 quintiles. &quot;These results confirm that reduced fetal growth is associated with increased risk of diabetes and suggest a specific association with thinness at birth. The relation seems to be mediated through insulin resistance rather than through impaired β cell function and to depend on an interaction with obesity in adult life.&quot;</td>
<td>In this cohort as with other studies, reduced fetal growth predicts insulinemia and impaired glucose tolerance but not the dyslipidemia characteristic of insulin resistance syndrome.</td>
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<td>The Bienestar Health Program</td>
<td>102 Mexican American fourth grade students, avg. age 9.2 yr, 54%♀, attending classes in two schools in San Antonio, TX. Their average BMI was in the 60th centile; compared to the USDA dietary guidelines, intakes of fat were higher and of fruits and vegetable were lower than recommended; 50% had a family history of diabetes.</td>
<td>The intervention extended over a nine month period. Separate instructional programs were administered to parents, teachers, school cafeteria workers, and after-school caregivers. Variables monitored included body fat, level of activity, fat servings, fruit and vegetable servings, total fat, fiber, cholesterol, health knowledge, and self-esteem. Dietary intake was measured by three 24-hr recalls.</td>
<td>This preliminary report found significant decreases in dietary fat intake and increases in fruit and vegetable intake. There was no significant difference in body fat or level of activity. Diabetes health knowledge was significantly enhanced. There were no changes in self-esteem scores.</td>
<td>Without reference data or control groups, it is hard to put the lack of change of body fat in perspective. As a preliminary study, this was intended to uncover difficulties and optimize the design of subsequent studies.</td>
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<td>The Kahnawake Schools Diabetes Prevention Project (Macaulay et al., 1997)</td>
<td>399 students age 6 - 12 yr, 197 9 , 182 6 . All attending the same Kahnawake School. All are of Native (Mohawk) heritage.</td>
<td>The intervention included health education programs at school, community-wide fitness programs, efforts to increase community awareness, and restrictions in foods offered in school. This is a mixed longitudinal, cross-sectional study. At baseline all students were evaluated. Children in grades 1 and 2 form a cohort that was followed annually for 2 subsequent years. Fitness and body composition measures included weight, height, triceps and subscapular skinfolds, and waist and hip circumferences. Behavioral measures included self-reported dietary and physical activity patterns. Proximal impact variables measured included self-efficacy and perceived parental support.</td>
<td>Only baseline data were reported in this publication. &quot;As expected anthropometric data increase with age. Between 9 and 10 years there are increased weight, height, BMI, and skinfold thicknesses; decreased fitness; and increased television watching. Implementing a Native community-based diabetes prevention program is feasible through participatory research that incorporates Native culture and local expertise.&quot;</td>
<td>Lack of controls allows only limited interpretation of the data. The results of the intervention are not reported.</td>
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<td>Jump Into Action Program (Holcomb et al., 1998)</td>
<td>1,114 fifth grade students at 14 schools in Webb County, TX. 91.3% were Hispanic, 5.7% non-Hispanic and 3% other. Nearly all were between ages 10 and 12. 51.8% , 48.2% . 30 teachers participated.</td>
<td>Students and teachers were separated into two groups. One group of teachers received training in diabetes prevention principles and how to use the Jump Into Action teacher’s guide and student workbook. Both groups were provided with the Jump Into Action program materials which were designed to improve student’s knowledge, self-efficacy, and behaviors regarding NIDDM prevention. Students and teachers were surveyed at the outset and conclusion of the evaluation period and again after 4 weeks post test. Outcomes for students included diabetes health knowledge, prevention knowledge, dietary intake, and physical activity. Outcomes for teachers included opinions on the effectiveness of the program, and willingness to recommend it.</td>
<td>Significant effects were observed for knowledge and self-efficacy gains and for healthy dietary and exercise-related behavior changes. Further changes from post-test to follow-up were observed for knowledge about the causes of diabetes as well as for diet and exercise self-efficacy. Small but significant improvements were noted in dietary fat intake and self-reported exercise. “Dietary behavior improvements were smaller than gains in knowledge and self-efficacy. For greater behavior change to flow from gains in knowledge and skills, other behavior modification techniques may be required.”</td>
<td>Factors limiting the reliability of the results include: the experiment contained no true control group; teachers and students were volunteers, not randomly assigned; incomplete survey responses limited the power of the exam; and there was a possible response bias from administering the same exam three times in a five month period.</td>
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<td>The Quest Program (Cook &amp; Hurley, 1998)</td>
<td>200 families of Native American (Pima) children in grades K-2 living and attending school in the Gila River Indian Community</td>
<td>Designed as a pilot program the goal was to develop skills in children to maintain a healthy body weight by diet and exercise and to promote awareness among the parents and community members that diabetes can be controlled. The program included: a series of anthropometric and biochemical tests, classroom instruction about diabetes prevention, increased daily physical activity during the school day, and structured school breakfast and lunch to support low-fat, controlled-carbohydrate meals.</td>
<td>The authors report difficulty in modifying the caloric intake of the children in the breakfast and lunch program and meeting federally mandated dietary guidelines for the Nu-Meals programs. The high caloric level of the Nu-Meals program is a problem for the severely obese and hyperinsulinemic subject group.</td>
<td>No outcomes or results included in this preliminary report.</td>
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<td>The Zuni Diabetes Prevention Program (Teufel &amp; Ritenbaugh, 1998)</td>
<td>83♀ and 90♂ Native American (Zuni) and Caucasian children attending grades 9-12, mean age 17-18 yr.</td>
<td>Five primary risk factors were targeted: obesity and pattern of fat distribution; insulin resistance (hyperinsulinemia); low physical activity, high consumption of sugared beverages, and low consumption of high-fiber foods (fruits and vegetables). Support networks were established, education programs developed, a wellness facility was constructed for physical activity, the food supply was modified (only sugar-free beverages were available, snack vending machines were eliminated, and fruit and vegetable snacks were made available). Outcomes assessed include BMI, waist-hip circumference, bioelectrical impedance, oral glucose tolerance test, 24-hr dietary recalls, physical activity recalls, heart rate monitoring, exercise test and recovery heart rate, diabetes health knowledge, and self-efficacy questionnaire.</td>
<td>The program is designed to extend over four years; the midpoint results are reported in this publication. There was a downward trend that did not attain significance in both female and male BMIs. There were no significant differences in fiber intake but sugared beverage intake decreased. Sitting pulse rates, and fasting and postprandial insulin levels were significantly lower, and fasting glucose levels were significantly higher. This suggests a decline in hyperinsulinemia. “Using this approach, health promotion messages are not directive (i.e., “just say no”) but are ubiquitous, giving the impression that everyone and everything is changing in a healthy direction. Behavioral change is relatively easy and gradual.”</td>
<td>The publication reports only preliminary results; details are insufficient to properly evaluate the efficacy of the program.</td>
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CHAPTER 7. OSTEOPOROSIS

The Food and Nutrition Board (FNB) of the Institute of Medicine (IOM) has recently established the Dietary Reference Intakes (DRI) for calcium to replace the Recommended Dietary Allowances (RDA) (NRC, 1989). Along with more traditional evidence to support dietary requirements, the DRI process also includes consideration of evidence concerning the prevention of disease (IOM, 1997).

One of the diseases that was considered by the FNB DRI Panel was osteoporosis, defined as an increased bone fragility and increased risk of fracture as a result of bone mass more than 2.5 standard deviations below the mean for young adult women (IOM, 1997).

Among the questions that need to be addressed regarding the relationships between osteoporosis and diet including the potential of intervention in children are: what the risk factors/biomarkers are in adults, whether they appear in children and track; and what the dietary correlates are and whether they track?

A. BIOMARKERS IN ADULTS

The IOM Panel on Calcium and Related Nutrients concluded that there is no biochemical assay that directly reflects calcium nutritional status, nevertheless, the Panel recognized both bone mineral content (BMC) and bone mineral density (BMD), most commonly determined by dual x-ray absorptiometry (DEXA), as useful predictors of fracture risk and thus, potentially useful as biomarkers for osteoporosis in adults (IOM, 1997). The utility of BMC and BMD as biomarkers may be complicated by various technical issues including instrumentation-dependent differences in absolute values and differences among different skeletal sites and among different types of bone structures (IOM, 1997; Maynard et al., 1998).

Although factors of expense, invasiveness, and experimental complexity preclude their utility as screening tools, metabolic kinetics and balance studies using stable isotopes have been effectively employed to determine at-risk groups prior to the onset of osteoporosis (Wanstey et al., 1996). Stable isotope studies have also been useful in dissecting out the differences in calcium metabolism and retention/excretion balance that potentiate osteoporosis, thus identifying possible intervention strategies.

B. DO ADULT BIOMARKERS APPEAR IN CHILDREN? DO THEY TRACK?

1. Calcium requirements: effects of age, gender, ethnicity

Calcium absorption increases in early puberty. Abrams & Stuff (1994) found that fractional calcium absorption averaged 34% in early puberty in Caucasian girls consuming about 925 mg calcium/day, up from 28% in previous years, and then decreased to 25% two years later (Table 7-2). Peak bone mass is achieved at different ages at various sites (Anderson & Metz, 1993).
The calcium AIs \(^2\) for adolescent boys and girls are based on the achievement of maximal calcium retention, determined largely from studies on white girls aged 11-14 years (IOM, 1997). Martin et al. (1997), using DEXA to measure bone mineral content, found that the mean daily calcium retention of boys and girls aged 9.5-19.5 years was 282 mg and 212 mg, respectively. Peak calcium accretion occurs at an average age of 13 years in girls and 14.5 years in boys (IOM, 1997). In a metabolic study by Weaver et al. (1995) white adolescent girls were found to absorb and retain calcium more efficiently than young women.

In the Fels Longitudinal Study, 8-18 yr-old male and female children were evaluated from 1 to 7 times, over a period of eight years; significant differences in bone mineralization between males and females were recognized. For males, BMC and BMD increased rapidly after age 12 yr, while females generally reached a plateau at approximately 14-15 yr of age (Maynard et al., 1998). Although this was a longitudinal study, no attempt was made to evaluate tracking, nor were dietary intakes reported. The fact that each subject was measured several times during growth leads to decreased experimental variance and allowed for sharper distinctions.

Racial differences in calcium metabolism during adolescence have been reported. Black adolescents may absorb calcium more efficiently and excrete less calcium in their urine than white adolescents (Abrams et al., 1996; Bell et al., 1993), which could explain the higher bone mass found in black children (Bell et al., 1991) and their lower bone-fracture rates as adults (IOM, 1997). One study found that calcium retention in black girls did not decline after menarche as it does in white girls (Abrams et al., 1995). In the judgment of the FNB’s Panel on Calcium and Related Nutrients responsible for generating the DRI, the implications of these differences in calcium metabolism for calcium requirements are not clear, so race-specific recommendations for this nutrient have not been made (IOM, 1997).

2. Biomarkers and intake

BMD, BMC, computed tomography (CT), and stable isotope studies have been employed in many cross-sectional epidemiological, cohort, and intervention studies in children. As noted above, the use of each of these techniques has its own advantages and disadvantages as biomarkers for all age groups. For example, change in BMD may be a less suitable in young children than change in BMC because it misses much of the change in skeletal size (IOM, 1997).

O’Brien et al. (1998) addressed the effect of heredity on the responsiveness of bone turnover to alterations in dietary calcium intake in girls and adult women from families with histories of osteoporosis. They found that granddaughters (age 8-15 yr), mothers (age 32-47 yr) and grandmothers (age 56-82 yr) from families in which one member had diagnosed osteoporosis had altered bone turnover responses to acute changes in calcium intake when compared to matched control non-osteoporotic families (O’Brien et al., 1998). The girls had higher rates of calcium deposition into bone, resorption from bone and net calcium balance than either the mothers or grandmothers. The number of subjects (five in each experimental group) limited the strength of the conclusions. Further studies are needed to confirm the effects in a larger sample of girls from osteoporotic families and to determine in the effects persist over longer periods of time. Though it is possible to draw inference about tracking from this study, the study was not designed to address the tracking per se.

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\(^2\) The Panel on Calcium and Related Nutrients of the FNB determined that “because of the methodological limitations in estimating precisely the dietary calcium intakes needed for maximal calcium retention in all age groups—an estimated average requirement (EAR) could not be derived with sufficient confidence, Thus, an Adequate Intake (AI) [was] estimated pending the development of a more comprehensive data base.”
Wastney et al. (1996) compared calcium kinetics and balance using stable isotope techniques in girls (age 11-14 yr) and women (age 19-31 yr). Girls absorbed more calcium from the diet, deposited more calcium in bone, resorbed more calcium from bone, and had a higher net calcium balance than women.

The differences in calcium kinetics and bone metabolism between adolescents and adults have been consistently demonstrated in a variety of cross sectional studies as reviewed in the DRI and NIH reports (IOM, 1997; NIH, 1995). Assumptions developed from epidemiological and cross-sectional studies are of moderate value in drawing conclusions about tracking. To address the tracking of biomarkers there is no real substitute for well-designed longitudinal studies evaluating BMC, BMD and or calcium metabolism in the same subjects.

C. DIETARY LINKS TO BIOMARKERS: DO THEY TRACK?

The dietary recommendations of the NIH and FNB are stratified by life-stage (i.e., age, gender, and reproductive status) and based on studies focused on BMC, BMD and calcium balance. (IOM, 1997; NIH, 1995). From a review of the evidence accumulated by the second and third National Health and Nutrition Examination Surveys (NHANES II and NHANES III), it has been concluded that many Americans do not meet current recommended guidelines for calcium intake and thus, remain at risk for developing osteoporosis (NIH, 1995).

1. Exposure: epidemiology of calcium intake

As can be seen in Table 7-1, a substantial proportion of children do not meet currently recommended guidelines for calcium intake and contemporary 6- to 11-yr-old children may even show a decreased calcium intake compared to those measured a decade earlier (NIH, 1995). This latter contention is supported by the data supplied by Albertson et al. (1997) who reported significant declines in calcium intakes over a ten-year period, particularly for adolescent girls aged 15 to 18 years. Moreover, the percentage of adolescent girls who consumed less than two thirds of the RDA (NRC, 1989) increased with age reaching 77% of 15 to 18 year old girls evaluated during the period of 1990-1992 (Table 7-2). Concerns about the intakes of adolescents have been reinforced by data collected for the USDA CSFII (1994-1996), documenting that only 36% of males and 14% of females adolescents consumed diets meeting the RDA for calcium.
Table 7-1. Calcium intakes of children 0-19 years of age and percentages meeting 1989 RDAs

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean calcium intake (mg/day)</th>
<th>Percentage meeting 100% of the 1989 RDA (%)</th>
<th>1989 RDA and 1997 AI (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants under 1 yr²</td>
<td>664</td>
<td>72.4</td>
<td>RDA: 400 (0-6 mo) 600 (6-12 mo)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>AI: 210 (0-5 mo) 270 (6-12 mo)</td>
</tr>
<tr>
<td>Children 1-2 yr</td>
<td>848</td>
<td>48.7</td>
<td>RDA: 800 AI: 500</td>
</tr>
<tr>
<td>Children 3-5 yr</td>
<td>819</td>
<td>43.5</td>
<td>RDA: 800 AI: 500 (3 yr) 800 (4-5 yr)</td>
</tr>
<tr>
<td>Children 6-11 yr</td>
<td>970 (males) 857 (females)</td>
<td>55.5 (males) 42.5 (females)</td>
<td>RDA: 800 (6-10 yr) 1,200 (11 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>AI: 800 (6-8 yr) 1,300 (9-11 yr)</td>
</tr>
<tr>
<td>Adolescents 12-19 yr</td>
<td>1,145 (males) 771 (females)</td>
<td>36.3 (males) 13.5 (female)</td>
<td>RDA: 1,200 AI: 1,300 (12-18 yr)</td>
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<tr>
<td></td>
<td></td>
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<td>1,000 (19 yr)</td>
</tr>
</tbody>
</table>

¹ Data are from CSFII, 1994-96. CSFII (Continuing Survey of Food Intakes by Individuals) is conducted by the Agricultural Research Service of the U.S. Department of Agriculture. Data presented above are the combined results from the 1994, 1995, and 1996 surveys based on respondents' intakes on the first surveyed day (U.S. Department of Agriculture, USDA). Food Surveys Research Group. Agricultural Research Service, 1997.

² Data exclude breast-fed infants.

³ Data are based on respondents' 2-day average intakes.

⁴ RDAs (NRC, 1989) and AIs (IOM, 1997) are issued by the Food and Nutrition Board of the Institute of Medicine, National Academy of Sciences.

2. Evidence of tracking

Several studies have been designed to address the question of tracking of calcium intake (Table 7-2). One study was found in which significant positive correlations were found for calcium intake at all time periods for which there were data, specifically in children between 4 and 15 years of age (Boulton et al., 1995). However, both Heaney et al. (1990) and Welten et al. (1995) described difficulties in the reliability and validity of retrospective methods for assessing calcium intake. Welten et al. (1997) concluded that "the predictability of calcium intake over time does not seem sufficiently strong to identify teenagers who are likely to maintain an inadequate calcium intake in adulthood. Therefore, the identification and treatment of subjects with a low calcium intake cannot be limited to the teenage period but should be extended into adulthood." Heaney et al. (1990) observed that based on their analyses of retrospective dietary intake data, "... accurate longitudinal estimates of intake require continuous, prospective monitoring and that, current intake is not a good estimator of past intake for most nutrients, especially for calcium."

As a consequence of both the lack of studies specifically designed to address the tracking issue and methodological difficulties associated with the collection of retrospective dietary data, little can be concluded
at this time about the tracking of calcium intake over time. What we do know is that data describing secular trends in dietary habits of children and adolescent indicate an insidious trend towards decreased consumption of calcium-rich foods, particularly in adolescent girls (Albertson et al., 1997). Aside from the limited data base on trends in food consumption patterns, little is known about the impact of either calcium fortification of foods or the use of dietary supplements on calcium intake of children and adolescents.

D. OPTIONS FOR INTERVENTION: POTENTIAL RISKS?

Of the many factors known to be associated with osteoporosis, dietary calcium levels has been identified as the most accessible for intervention and the preferred approach to obtaining optimal calcium intake is through dietary sources (NIH, 1995). It has been suggested that because of problems of bioavailability, difficulties in attaining recommended levels for some at-risk age groups and those on restricted diets, and other complications the consumption of calcium-fortified foods and calcium supplements may be required to meet calcium requirements. The NIH Consensus Development Conference (NIH, 1995) concludes “The task for individuals to meet calcium requirements on a continuing daily basis is a formidable challenge.” Because current dietary intake data indicate that calcium intake is below recommended levels, changes in dietary habits including increased consumption of dairy products and/or other calcium-rich dietary sources and/or supplements are recommended (NIH, 1995).

In addition to evidence indicating an inability of at-risk groups to met calcium intake requirements, concern has been raised about the impact of other dietary interventions on calcium status. Specifically, efforts to reduce dietary fat content of children’s diets could potentially lead to reduced calcium intakes as foods likely to be eliminated or reduced in such regimens are often the best sources of calcium. This concern is supported by the study by Johnson & Wang (1997) who evaluated the link between fat and calcium intake in children using the data from USDA CSFII (1989-1991). They reported that in children aged 5 to 17 years, calcium intakes were “higher in the high fat intake groups in comparison with low fat intake groups.” With regard to recommendations to lower fat is the diets of school-aged children, Johnson & Wang (1997) concluded that such recommendations “must be counterbalanced by guidance that promotes optimal calcium intakes.”

As discussed in the DRI report, the three major hazards associated with excess calcium intake have been primarily the result of intake from nutrient supplements (IOM, 1997). Kidney stone formation, milk-alkali syndrome, and the interaction of calcium with the absorption of other essential minerals have each been associated with excess calcium intake but the associations are confounded by other variables including other dietary factors, age, and sex. The association between calcium intake and kidney stones is weaker in children than adults and there have been no reported cases on milk-alkali syndrome in children (IOM, 1997).

Calcium has been shown to interact with iron, zinc, magnesium and phosphorous metabolism (IOM, 1997). Because calcium interferes with several nutrients simultaneously, it is difficult to quantify its effect on any one mineral. However, because these minerals are essential for growth and development this is accepted as a potential risk rather than an adverse effect. Potential at-risk groups include growing children, populations on very low mineral intakes, and the elderly.

Both the IOM and NIH reports recommend upper limits for calcium ingestion to prevent these complications. Recognizing the variability in needs and risk between different populations, both reports include recommendations for more research on the long-term effects of calcium intake on regional changes in bone
mass and fracture incidence, achievement of peak bone mass, bone remodeling, adverse effects of high intakes, and the interactions with other interventions (IOM, 1997; NIH, 1995).

E. SUMMARY AND CONCLUSIONS

In the NIH Consensus Development Conference on Optimal Calcium Intake report, several studies were cited in which certain at-risk groups were shown to be in negative calcium balance (losses exceeded intake) despite having intakes that met or exceeded recommended levels. Women in the first 6-8 years after the onset of menopause have a net negative calcium balance and loss in BMC and BMD associated with the declining estrogen levels. This loss in BMC and BMD can be slowed but cannot be reversed by increased dietary calcium intake (NIH, 1995). After the period when estrogen deficiency is no longer dominant (approximately 10 years after menopause), increased dietary calcium is somewhat more beneficial in slowing bone loss (NIH, 1995). However, for each individual there is a plateau, above which increased dietary intake of calcium has no further beneficial impact on BMC or BMD (IOM, 1997). Other factors including dietary constituents, estrogen replacement, vitamin D supplementation, and exercise have been shown to affect bone loss (IOM, 1997; NIH, 1995; Teesalu et al., 1996). Even under conditions when calcium intakes and other factors have been optimized for preventing bone loss, osteoporotic post-menopausal women have been shown to have negative net calcium balance (O'Brien et al., 1998). Because there are clear limitations to preventing bone loss via interventions in adults, attention has turned to interventions begun earlier in life, i.e., increasing calcium reserves to build stronger bones during childhood. The NIH Consensus Development Conference asserted that two factors that influence the occurrence of osteoporosis are optimal peak bone mass attained in the first two to three decades of life and the rate of bone loss in later years (NIH, 1995).

Of the studies on calcium balance, bone mineralization, and bone strength in children, few have been designed to address tracking and long-term consequences, and fewer still have studied tracking from adolescence to adulthood, the period when peak bone mass is achieved. Such tracking studies have important implications to public health policy. If calcium intake does track from youth to adulthood, subjects at risk for calcium deficiency can be identified at an early age. Moreover, strategies could be developed to ensure that interventions such as increased dietary intake of calcium, initiated early in life, persist over time. One obstacle confronting those that might pursue an examination of the tracking question is that current intake may not be an accurate reflection of past intake (Heaney et al., 1990). A position further reinforced by the report by Welten et al. (1997) who found that in their cohort calcium intake showed only "moderate" tracking from adolescence through to adulthood. As noted previously in Chapter 2, both Heaney et al. (1990) and Twisk et al. (1997) have reported difficulties in assessing long-term calcium intake.

Studies of calcium supplementation in children have yielded fairly consistent results. In the selected examples in this review, increased daily calcium intake in the form of dairy milk resulted in significant increases in BMD and BMC growth for 12 yr-old females (Cadogan et al., 1997), and increased dietary calcium resulted in an increased net calcium balance in 8- to 15-yr-old females from both osteoporotic and non-osteoporotic families (O'Brien et al., 1998). Previous studies have shown that BMD declines shortly after acute interventions cease (IOM, 1997; NIH, 1995). Thus, acute intervention in children in the absence of long-term strategies for maintaining calcium balance is of unproven benefit.
Table 7-2: Studies of Osteoporosis Risk Factors and Calcium Intake in Children

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>Subject Number and Description</th>
<th>Methods Outcome Variables</th>
<th>Results and Authors' Conclusions</th>
<th>Comments</th>
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<tr>
<td>Abrams &amp; Stuff, 1994</td>
<td>Using public advertising, 51 white females (age range 4.9-16.7 y) were enrolled in this study. Subjects were not using steroid hormones or mineral supplements. Based on interviews subjects were divided into three groups based on menarche: prepubertal (n=21; mean age 7.7 y), early pre-pubertal (n=13; mean age 10.9 y), and late pubertal (n=17; mean age 15.2 y)</td>
<td>The study was designed to evaluate calcium metabolism in females aged 5-16 y consuming self-selected diets. Dietary data were collected before the study (a single 24-hour recall that was used to establish the intake during the trial). Three day diaries (beginning on the day of the trial) were also collected. Protocol: Study took place in a metabolic ward. Subjects were served breakfast concluding with a glass of milk containing stable isotope &quot;Ca followed by intravenous (IV) infusion of another stable isotope &quot;Ca. Fasting blood sample was collected prior to challenge to assess routine biochemical measures.</td>
<td>- Calcium intakes were similar among subjects irrespective of age or pubertal development. - Intakes were below the RDA in 21 of 25 subjects ≥11 y. - Percent dietary calcium absorption was highest in the early pubertal group, followed by pre-pubertal and late pubertal groups. - Calculate mean calcium retention was 132 mg/d in pre-pubertal, 161 mg/d in early pubertal and 44 mg/d in late pubertal subjects. - Calcium absorption was not related to urinary calcium excretion. &quot;We conclude that peak periods for calcium retention for girls are in the pre- and early pubertal periods.&quot; &quot;The current calcium intake of American girls during the pubertal growth period may not enable maximal mineral retention; therefore, increased calcium intakes should be considered.&quot;</td>
<td>Aside from being characterized as &quot;white&quot; the racial makeup of the subjects, e.g., Hispanic versus non-Hispanic Caucasian, was not provided. Relied solely on a single 24-hour recall to assess &quot;usual&quot; calcium intake. This estimate was then used to determine calcium content of the challenge (1/3 of usual daily intake). No analyses were presented to evaluate the range of usual intakes (i.e., prior to the study) among study participants.</td>
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<tr>
<td>Study (Reference)</td>
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<td>Abrams et al., 1995</td>
<td>Data from a total of 89 ♀ (38 black, 51 white; ages 4.9-16.7) were included in this report. The data from the white subjects are those included in Abrams &amp; Stuff (1994).</td>
<td>See Abrams &amp; Stuff, 1994 Rather than dividing subjects into groups based on pubertal stage, the investigators made comparisons were made based on monarchal status (pre- versus post-menarche) and race using 2-way analysis of variance.</td>
<td>The post-menarche white group was significantly older (mean ages 15.4 versus 13.3) and taller (165 cm versus 160 cm) than the corresponding black group. (Although not discussed, calculated BMI of black group was 21.3 versus 19.9 in white)</td>
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<td>- Both pre- and post-menarche black girls had significantly greater fractional calcium absorption than white girls in the same groups.</td>
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<td>- Fractional absorption was more closely correlated to calcium intake in white versus black girls.</td>
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<td>- Total calcium absorption was greater in black than in white post-menarche girls</td>
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<td>- Urinary calcium excretion was significantly greater in black than in white pre-menarche subjects.</td>
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<td>&quot;Calcium kinetic values associated with bone calcium deposition were greater in black girls indicating a greater rate of bone calcium deposition in both pre- and post-monarchal black girls. These results suggest that the greater bone mass accumulated during childhood and adolescence in black than in white females is due, in part, to</td>
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See Abrams & Stuff, 1994 Because of the significant differences in age between the two post-menarche groups in this report, the differences in calcium retention etc. reported in this report could be questioned based on the differences between early pubertal and late pubertal groups reported in (Abrams & Stuff, 1994) (i.e., differences in calcium kinetics between early and late pubertal girls).
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<tr>
<td>Fels Longitudinal Study (Maynard et al., 1998)</td>
<td>148 healthy, white children between 8-18 yr old, between 30 and 100 kg bw, and &lt;190 cm in stature. The 8-9 yr-olds were in the uppermost quartile for stature and weight. A total of 465 annual examinations were included in the study; the number of examinations per child ranged from 1 to 7.</td>
<td>Bone mineral content (BMC) and bone mineral density (BMD) was measured using a Lunar DPX dual x-ray absorptiometer (DXA). BMC and BMD were determined for total body, head, arms, spine, pelvis and legs.</td>
<td>&quot;...boys and girls showed similar increases in BMC of the total body, arms, legs, and pelvis until ~12 y of age. In boys, BMC and BMD increased rapidly after age 12 y, whereas girls generally reached a plateau at ~14-15 y of age after which further increases in BMC and BMD were minimal.&quot; There were significant sex differences in BMC and BMD after the age of 11 y among the various anatomic measurement groups.</td>
<td>Cross comparison between different BMC and BMD studies are difficult as a result of confounding measurement artefacts. Major factors contributing to these differences are differences in instrumentation and the choice of anatomic boundaries to define skeletal region.</td>
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</table>

"Despite differences in absolute values obtained from different populations using various DXA instruments, overall patterns of bone mineral acquisition throughout childhood are consistent across investigations."

"sex differences in the accrual of BMC and BMD occurred ~ 1 y and ~ 2 y, respectively, after the age of peak height velocity" (puberty)
<table>
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<tr>
<th>Study (Reference)</th>
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<tr>
<td>Cadogan et al., 1997</td>
<td>82 healthy, white girls aged 12.2 y recruited from four Secondary schools in UK. 80 subjects completed the trial.</td>
<td>In this 18 mo-long randomized intervention trial, subjects were stratified by pubertal stage. The intervention group consumed 568 ml milk, either whole or reduced fat milk according to the subject's preference, as a supplement to usual food intake. Dietary intakes were assessed by 7 day weighed intake method at the baseline and conclusions, supplemented with 4 d non-weighed food diaries on 5 interim occasions. Outcomes assessed at 0,6,12, and 18 mo included: BMC and BMD, assessed by DEXA; anthropometric and body composition variables, biochemical markers of bone turnover (osteocalcin, bone alkaline phosphatase, deoxypyridinoline, type I collagen N-telopeptide), and skeletal growth hormones (PTH, estradiol, IGF-I).</td>
<td>Daily milk intake at baseline was 150 ml for both groups; the intervention group consumed, on average, an additional 300 ml a day throughout the trial. Compared with the control group, the intervention group had greater increases in BMD (9.6% v 8.5%), BMC (27% v 24.1%), and serum IGF-I (35% v 25%). Intakes of protein, calcium, phosphorus, magnesium, zinc, and riboflavin in the intervention group were significantly higher than the control group. “Increased milk consumption significantly enhances bone mineral acquisition in adolescent girls and could favorably modify attainment of peak bone mass.”</td>
<td>The effect of increased intake of calcium cannot be resolved from that of protein and other nutrients. Results consistent with evidence from calcium supplementation trials in children and adolescents, dairy supplementation trial in early pubertal girls and retrospective studies. The intervention group ingested either whole or reduced fat according to the subject’s preference. The effect of fat ingestion in those choosing whole milk was not evaluated, although fat affects calcium absorption. Short term increases in calcium may not sustain increased bone mass over longer periods of time. Increased protein intake may lead to increased calcium excretion rates (Appleby, 1998). Because, the intervention group had lower BMC and BMD at baseline, these data may reflect catch up growth (Eastell et al., 1998).</td>
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<td>Gilsanz et al., 1998</td>
<td>80 healthy, black and white children matched by chronological age, gender, Tanner stage, height, and weight. 40 pairs of boys and 40 pairs of girls.</td>
<td>- Bone density and cross-sectional area was measured by quantitative computed tomography (CT) in vertebrae and femurs. - Blood levels of calcitropic hormones, growth hormones and sex steroids were determined. - Biochemical measures of bone metabolism were determined in blood (PTH, 25-hydroxy- and 1,25-dihydroxy-vitamin D, alkaline phosphatase, bone-specific alkaline phosphatase, calcitonin, IGF-I, osteocalcin) and urine(pyridinoline and deoxypyridinoline).</td>
<td>CT allows the distinction between cancellous (less dense, lattice-like core region) from cortical (very dense, outer region) bone. &quot;Race had a significant and differential effect on the bones in the axial and appendicular skeletons. In the axial skeleton, black children had greater cancellous bone density, but similar cross-sectional area of the vertebral bodies. In contrast, in the appendicular skeleton, black children had greater femoral cross-sectional area, but similar cortical bone area and cortical bone density. Compared to white children, vertebral bone density and femoral cross-sectional area at sexual maturity were, on the average, 10.75% and 5.7% higher, respectively, in black children.&quot; Previous studies suggest that and growth of the axial and appendicular skeletons are probably regulated under different hormonal control. However, there were no differences observed in the serum levels of hormones, growth factors or sex steroids between black and white children in this study. Compression strength in the vertebrae is determined by the density of cancellous bone and its cross-sectional area. In the femur, the greater cross-sectional area and similar cortical bone area in black children compared to white children would manifest as reduced cortical thickness placed further from the center of the bone and result in a bone of greater strength.</td>
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<td>Study (Reference)</td>
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| Jackman et al., 1997   | 21 subjects were included in the crossover study. Inclusion criteria: white ♀ aged between 12-14 year; BMI between 15th and 85th percentiles, no medical problems or use of medications including oral contraceptives, a usual calcium intake ≥ 800 mg/d (based on three 24-hr dietary records), no history of pregnancy or abortion, no past or current eating disorder and no history or current use of tobacco. Data from an additional group of 14 ♀ consuming one level of calcium intake (1332 mg/d) under similar conditions as those in this protocol were also included. | The study was intended to “describe the relation between calcium retention and dietary calcium intake in adolescent girls aged 12-15 y who had calcium intakes ranging from 841 to 2173 mg/d ...”  
“Subjects were stratified to groups on the basis of baseline serum osteocalcin concentrations, BMI, and post-monarchal age...”  
The study was a randomized blinded crossover design in which subjects received either a high or low calcium diet. The majority of calcium in basal diets came from dairy sources. Differences in the high intake condition were accomplished using a fruit-flavored calcium fortified beverage.  
Subjects were housed in campus residence for two 21-day balance studies. (7-d acclimation, 14-d experimental period). 4-week washout period. | Mean maximal calcium retention across all groups was 473 mg/d.  
“At higher post-monarchal ages, maximal calcium retention was lower but the intake required to achieve this was not affected.”  
Calcium intake explained 79 and 6% of the variation in fecal and urinary calcium excretion, respectively.  
At intakes of 1200 mg/d a mean calcium retention of 57% of maximal value was found.  
The lowest intake at which at least some of the subjects attained 100% of maximal calcium retention was 1300 mg/d. Retention continued to improve at intakes > 2000 mg/d. | Subjects were grouped into four different high versus low calcium intake categories. Descriptive statistics were presented only for the whole group.  
Deionized water was the used throughout the study periods. Discretionary use of table salt was not allowed.  
Diets were designed to be constant with regard to total nitrogen (and calculated protein), phosphorus, and total fat content. No significant differences between the balance periods were reported for these nutrients.  
Although diets were designed to be constant actual intakes were not compared.  
No attempt was made to document intakes during the washout period. |
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<tr>
<td>O'Brien et al., 1998</td>
<td>Ten Caucasian families grouped according to bone status as either control (n=5) or osteoporotic (n=5). Each family was represented by the grandmother (GM; age range 56.2-81.7 y), mother (M; age range 32.1-47.1 y), and granddaughter (GD; age range 8.2-15.3 y). Control families had no history of low bone mass. Families were classified as osteoporotic if either the M or GM had a total BMD, or lumbar spine BMD greater than or equal to 2 SD below the average. Control and osteoporotic females were comparable with respect to age, height, weight, and BMI within each generation group. GMs and Ms were matched for menopausal status, GDs were matched for monarchal status.</td>
<td>Families consumed either a low- (approx. 250 mg/day) or high- (approx. 1500 mg/day) Ca for 15 days. Diet was assessed by 24-h dietary recalls (3) during the dietary period and a weighed dietary record on the day of the isotope study. Calcium absorption and metabolism were evaluated using stable isotopes of Ca administered orally and intravenously. Outcome variables included: serum and urinary calcium levels, and various biochemical and hormonal indices of bone metabolism. Serum and urinary calcium data were fit to a multi-compartmental model to estimate calcium kinetics.</td>
<td>Both girls and adult women in the osteoporotic families had significantly increased bone calcium deposition and resorption during the high-calcium period which lead to “a less positive balance in bone calcium turnover.” Calcium absorption was significantly lower during the low-calcium diet. “This is of concern, given that on any one day, 25% of U.S. women consume calcium intakes below this level.” Intestinal calcium absorption was significantly related to age, decreasing with increasing age during the period of low dietary calcium intake. Although, increasing dietary calcium improved calcium retention in all age groups, the authors found: “Adult and elderly women from osteoporotic families were unable to maintain a positive calcium balance during the high-calcium period.” “In summary, optimum calcium intake should be provided to young girls, especially those that have a family history of low bone mass, to assist in the attainment of peak bone mass and the prevention of future osteoporosis.”</td>
<td>Differences in calcium turnover as a response to acute changes in calcium intake appear to track across generational lines in osteoporotic families. Girls in osteoporotic families showed a trend towards lower balance in calcium turnover during high-calcium intakes than the control girl group. Further studies with larger study population are required to confirm these results or to determine if the trends persist after prolonged periods of calcium intake.</td>
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<td>Study (Reference)</td>
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<td>Teesalu et al., 1996</td>
<td>Children 10-14 yr of age (n=22) and postmenopausal women 50-60 yr of age (n=11) assigned into two groups: lactase-normal and lactase-deficient.</td>
<td>Calcium, dairy intake and the presence or absence of intolerance to milk and dairy products was ascertained by interview. Urinary excretion of calcium, serum calcium, serum phosphate, PTH and calcitonin were measured. Osteoporosis was ascertained by a history of fractures related during interview.</td>
<td>&quot;Lactase deficiency appears to be one of several factors that predispose the development of osteoporosis, probably through diminished calcium intake.&quot; In children and post-menopausal women with lactase deficiency and osteoporosis the mean value of calcium intake was smaller than in the lactase-normal group (540-670 vs 820 mg/day) and (630 vs 1200 mg/day) respectively.</td>
<td>The results are difficult to evaluate because experimental detail and statistical significance of the results are not reported.</td>
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<td>Wastney et al., 1996</td>
<td>Healthy adolescent (n=14) and adult (n=11) white females. The adolescents included 5 premenarcheal, five less than or equal to 1 yr post monarchal, and 4 1-3 yr postmenarche. The women were 4-19 yr postmenarche</td>
<td>After 7 days on a diet containing 1330 mg calcium/day two stable isotopes of calcium were administered, one orally and one intravenously, and blood, urine and feces were collected for 14 days. During the entire 21 day experiment, the diet was controlled but the subjects otherwise simulated a free living environment. Serum, urine and fecal calcium data were fit to a three-compartment describing calcium kinetics. The compartments do not correspond directly to anatomic spaces. The first compartment includes the blood and other rapidly exchangeable spaces, the second is considered to be soft tissue and the third, exchangeable calcium on bone.</td>
<td>Apparent differences in calcium kinetics resulted in significantly higher amounts of calcium in both the second and third compartments in girls than in women. Girls absorbed more calcium from the diet, excreted less calcium in urine, deposited more calcium in bone and resorbed more calcium from the skeleton. “Girls retained more calcium than women (282 vs -41 mg/day) through increased absorption, lower urine excretion, and higher bone turnover.</td>
<td>Studies such as these can help identify critical differences in adolescent bone metabolism and potential points of intervention to maximize the accretion of bone mass during the growth period.</td>
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<td>Adelaide Nutrition Study (Boulton et al., 1995)</td>
<td>The subjects were drawn from the Adelaide Nutrition Study in Australia. Subjects (n=106) were recruited at birth and followed through age 15 y. An additional group (n=123) were added beginning at age 11; also followed through age 15 y.</td>
<td>This report includes data from a larger study on tracking of risk factors for ischemic cardiovascular disease. Tracking was defined as “the correlation coefficient between age points, e.g., 2-8 y, 2-11 y...” In addition to fasted blood samples collected at 1 and 2 years of age and annually thereafter, 4 day weighed food records (3 weekday, 1 weekend) were collected annually. Two different databases were used for nutrient analysis over the course of the study.</td>
<td>“Tracking of dietary calcium was stable between intervals from 4 years of age, but there was a greater degree of continuity from 6 to 11 years onwards and from 8 to 11 years onwards than for energy or fat, particularly for males. There was an equal degree of drift downwards for those in the top quintile at 4-8 and 8 and 15 years of age as there was upwards for those in the bottom quintile for both absolute calcium intake and calcium density (mg/mL).” All time periods for which there were data, i.e. &gt; 4 y, were positively correlated (p&lt;0.001)</td>
<td>A comparison of the two nutrient databases revealed “minor differences” in calculations for fat content which “would not have affected the outcome of the tracking.” Actual data were not provided.</td>
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**Calcium Intake: Tracking**
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<td>Amsterdam Growth and Health Study (Welten et al., 1997)</td>
<td>182 subjects (84 ♂, 98 ♀) beginning 13 yr.</td>
<td>Dietary measurements were collected a total of 6 times over 15 year period; annually over the first four years (ages 13-17), once each at ages 21 and 27. Calcium and dairy intake was assessed by a cross-check dietary history method. Food frequency/dietary history was used with a one month reference period. Parents/caregivers were questioned about qualitative details, e.g., skim vs whole milk, etc. The longitudinal development of calcium intake excluding calcium supplement use, was analyzed for three different age periods, 13-17 yr, 17-21 yr, and 21-27 yr and compared to Dutch Recommended Dietary Allowances.</td>
<td>Calcium intake for both males and females increased about 30% over the 15 yr period. Intakes for the age period 13-17 yr decreased significantly for females but not for males. Although for the groups combined, a significant time effect was observed for the period 17-21 yr, there were no significant sex by time effects for the periods 17-21 yr or 21-27 yr. Throughout the period of 17-27 yr, males had significantly higher calcium intakes than females. Tracking of calcium and dairy intake was only moderately correlated from adolescence into adulthood in both sexes. The author's conclude “The predictability of calcium intake over time does not seem sufficiently strong to identify teenagers who are likely to maintain an inadequate calcium intake in adulthood. Therefore, the identification and treatment of subjects with a low calcium intake cannot be limited to the teenage period but should be extended into adulthood.”</td>
<td>Within-person variability may lead to underestimation of the real tracking phenomenon. This study attempts to partially correct for this variation. The results rely heavily on the limited data collected over the age of 16.</td>
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<td>The General Mills Dietary Intake Study (Albertson et al., 1997)</td>
<td>4,000 households were randomly selected households. Samples were collected for each of four two year collection periods. Samples were demographically matched.</td>
<td>This was a study of secular trends in calcium consumption patterns in adolescent girls. As such it included estimates of dietary calcium intake of three groups of adolescent girls during four separate 2 y periods during the period 1980-1992 and to identify food sources of calcium. Complete 14-day home and away from home food and beverage consumption records were collected for every member of each household. Records for girls 12-18 y were analyzed for this report. Data were stratified by three age groups: 11-12 y, 13-14 y, and 15-18 y. for each of the four time periods.</td>
<td>- Dietary calcium intake declined significantly over the 10 y period for 15-18 y olds - Calcium intake was significantly lower for 13-14 y olds compared to the youngest age group and was significantly lower in 15-18 y olds than either of the other age groups over the entire study period - Over 90% of all subjects consumed &lt; 100% of the 1989 RDA at all time points. - The % of subjects who consumed &lt;2/3 of the 1989 RDA increased with age, with 77% of 15-18 y olds below this level in the 90-92 time period. - Milk and milk products were the best sources of calcium, however the percentage contributed by this food group declined with age over time, due primarily to a decline in fluid milk consumption.</td>
<td>Data bases for nutrient content of diets were changed after the third time period. Periods 1-3 used Michigan State Univ. database, the fourth time period data set was analyzed using the Univ. Minnesota database. After “bridging analysis” to determine the impact of the switch in databases, it was determined that “less than 4% (or 1-3 mg) of the differences seen were accounted for by the database change.” No analyses by race or other demographic were presented.</td>
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| Heaney et al., 1990    | Data derived from two cohorts: 1) Roman catholic nuns (n=164) aged 35-45 part of a longitudinal study that began in 1967. 2) nulliparous students (n=165) recruited from local colleges, ages 19-25 when recruited and followed every 6 months for up to 4 y. | Group 1: collected 1 day diet diaries for the period 1967 through 1972, and a 7-d diary was used thereafter. Intakes included calcium containing medications and supplements.  
Group 2: collected 7-d diaries | Larger individual variability was noted even over short periods.  
"Over longer intervals, the predictive value of one estimate in respect to a second deteriorated even further." Consequently over a 5 y interval less than 25% of variability could be accounted for by present intake.  
Calcium was the “least consistent nutrient.”  
"These data show that accurate longitudinal estimates of intake require continuous, prospective monitoring and that, current intake is not a good estimator of past intake for most nutrients, especially for calcium." | Use of calcium containing medications and supplements were noted for Group 1; no such notation included for group 2.  
A number of nutrient databases and analytical approaches were used over the course of this study.  
"Between system consistency was assured at each transition by dual analyses for the nutrients of interest..." |
REFERENCES CITED


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