INSIDE

NUTRITION CLOSE-UP

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Birth Weight and Diet Sensitivity

A mother's nutritional status during pregnancy directly influences birth weight, which can have long-term effects on the health of her offspring. As discussed in the article by Painter et al. (see story on page 6), insufficient maternal intake can have a significant impact on risk factors for coronary artery disease (CAD). Emerging research also suggests that energy and nutrient intake during gestation and the resultant birth weight might also help determine physiological responses to dietary fat intake throughout life. For example, we recognize that plasma lipid levels vary widely between individuals in response to dietary intake. Although it is widely accepted that much of this variation is genetically determined, the other determiners of individual response to dietary factors are not well understood. One explanation for these disparities might be maternal nutrition during gestation. A recent study by Robinson et al. indicates that maternal nutrition status during pregnancy might modify individual physiological responses to dietary fat and saturated fat intake.

Men (n=547) and women (n=562) between the ages of 59 and 71 years who were born in Hertfordshire County, UK, and who still lived in the same county, were recruited for participation in this study. This location was chosen because of the detailed records kept by midwives in Hertfordshire County from 1911-1948. Birth weights had been recorded for all participants. Although a number of individuals were taking cholesterol lowering medications, potential participants with a history of CHD were excluded from the study.

Participants completed food frequency questionnaires to estimate typical intake of total fat and saturated fat during the three-month period prior to the interview. Each participant was interviewed at home, where information on dietary intake and medical history was obtained. Each participant underwent a fasting blood draw for measurement of HDL and LDL cholesterol levels. The ratio of HDL to LDL cholesterol was also determined for comparison.

These findings "suggest that adult cholesterol responses to dietary fat are conditional on birth weight, and hence prenatal growth, in men."

None of the measures of plasma cholesterol (including total, HDL, LDL cholesterol and the ratio of HDL to LDL cholesterol concentrations) were significantly related to birth weight or to fat intake. However, significant correlations emerged when the group of men was subdivided into tertiles based on birth weight. (No significant associations were seen in the women after they were similarly subdivided by birth weight.) In the group of men with the lowest birth weights (<3.2 kg or <7 lb), total and saturated fat intake was inversely associated with HDL cholesterol levels. In men in the highest tertile for birth weight (>3.65 kg or >8 lb), however, higher intakes of total and saturated fat were associated with higher HDL concentra-

tions (P for interaction = 0.02 for total fat and 0.03 for saturated fat intakes; P = 0.09 and 0.08, respectively, after adjustment for age, BMI, and alcohol intake.) These associations were strengthened after excluding men from the data set who were taking cholesterol reducing medications. HDL cholesterol levels were lower for men in the lowest tertile of birth weight and higher for men in the highest tertile of birth weight with the highest total and saturated fat intakes (P for interaction = 0.02 for total fat and 0.02 for saturated fat intake). The HDL:LDL ratio was lower for men in the lowest tertile and higher for men in the highest tertile of birth weight (P for interaction = 0.008 for total fat and 0.006 for saturated fat intake).

One mechanism that may explain these findings was described in a similar study using guinea pigs. Male guinea pigs whose mothers' diets had been restricted responded to a cholesterol challenge with higher plasma cholesterol levels than did male guinea pigs whose mothers had access to unlimited food during gestation. Plasma cholesterol levels were also found to be higher after the cholesterol challenge in the low-birth weight guinea pigs. Adult liver weights in the low-birth weight guinea pigs were also lower than in the higher-birth weight males. Liver weight in the low-birth weight males was found to be associated with lower HDL- and higher LDL-cholesterol levels following the cholesterol challenge.

It is thought that nutrient restriction during all or part of the gestational period might influence the size of the liver, which is the organ most responsible for cholesterol metabolism. This could explain why low birth weights in the present study were associated with altered cholesterol metabolism in adulthood. The authors conclude that their findings "suggest that adult cholesterol responses to dietary fat are conditional on birth weight, and hence prenatal growth, in men." ◾

Robinson SM, Batelaan SF, Syddall HE, Sayer AA, Dennison EM, Martin HJ, Barker DJ, Cooper C, and the Hertfordshire Cohort Study Group. Combined effects of dietary fat and birth weight on serum cholesterol concentrations: the Hertfordshire Cohort Study. *Am J Clin Nutr* 2006;84:237-44.

Kind KL, Clifton PM, Katsman AI, Tsiounis M, Robinson JS, Owens JA. Restricted fetal growth and the response to dietary cholesterol in the guinea pig. *Am J Physiol* 1999;277:R1675-82.

KEY MESSAGES

- Males (but not females) with the lowest birth weights responded to high intake of total and saturated fat with lower HDL levels and lower HDL:LDL ratios in adulthood.

- Inadequacy of calories and/or nutrients during all or part of the gestational period might cause adaptations in organ systems responsible for cholesterol metabolism. This could explain why low birth weight in the present study was associated with altered cholesterol metabolism in adulthood.

Taking a Closer Look at *Trans*-fats: *The Verdict is In, but is the Case Closed?*

Among modern nutrition fallacies, one of the most recent and most notorious was the assumption that all fats are created equal. Although the idea seems foreign today, it wasn't long ago that low-fat diet advice applied to all fats, without regard to source or saturation level. Saturated, polyunsaturated, monounsaturated fats…all were to be avoided in order to qualify in the healthy diet category. Industry scrambled to meet consumer demand and low-fat/fat-free products—often with added sugar—multiplied on supermarket shelves.

We are now in the midst of another industry scramble, this time to remove *trans*-fats from manufactured foods. Because *trans*-fatty acids (TFAs) have been shown to negatively affect cardiovascular disease risk factors, consumer demand for TFA-free products has escalated and industry is responding; but it should come as no surprise that new findings are causing some researchers to question the assumption that all TFAs are equally hazardous to human health. Just as there are many types of fat, there are numerous variations of TFA. Like total fat, TFAs can also be differentiated into several classes, based on chain length and saturation site. Take *trans*-18:2 and *trans*-18:1, for example—although both are TFAs, evidence suggests that each has a unique effect on heart disease risk.

In 2002, Lemaitre et al. published research examining the effects of different classes of *trans*-fatty acids on the risk of sudden cardiac death. To confirm and extend the findings of that study, the same research group designed a similar study using the same data set to determine the influence of two classes of TFAs—*trans*-18:1 and *trans*-18:2—on the risk of fatal ischemic heart disease (IHD).

Trans-18:1 is the predominant class of *trans*-fat formed during the hydrogenation process, although small amounts of *trans*-18:2 are also produced. *Trans*-18:2 is found in nonhydrogenated refined

oils (such as refined soybean, sunflower, corn, peanut, and canola oils, in which *trans*-18:1 fatty acids are generally present in only trace amounts) and in small amounts in some dairy products. *Trans*-18:2 can also be produced during the frying process, so food preparation also determines its presence in a food.

Using data collected during the large, multicenter Cardiovascular Health Study, Lemaitre et al. identified a sample of 214 men and women who had experienced fatal IHD events (including 95 sudden cardiac deaths) between June 1992 and June 1998 (cases). Individuals who did not experience fatal IHD events were selected and matched to cases based on age, gender, cardiovascular health status, clinic site, and other variables.

Because the lipid content of RBC membrane phospholipids reflects dietary intake, it can be used as a biomarker for this variable. Fasting blood samples that were collected an average of 3.0 ± 1.6 years prior to the fatal events were used to determine the *trans*-18:1 and *trans*-18:2 content of RBC membranes. Participants provided medical history and health status information at the time of the blood draw and blood pressure was also measured. A subset of participants completed a food frequency questionnaire approximately three years prior to the blood draw.

Mean RBC levels of TFAs were similar between cases and controls, as were age and sex distribution, and history of CHD. Participants were divided into quintiles of membrane TFA levels. Those in the highest quintile for *trans*-18:1 had lower mean insulin levels (9.9 μ/mL vs. 17.7 μ/mL, respectively). Multivariate analysis demonstrated that although total TFA was not related to the risk of fatal IHD, higher levels of *trans*-18:2 were associated with greater risk of a fatal IHD event. For increasing levels of *trans*-18:2, risk estimates were as follows: 1.0 (reference); 0.87 (95% CI 0.41 to 1.84); 1.08 (95% CI 0.52 to 2.28); 3.20 (95% CI 1.42 to 7.20); 4.52 (95% CI 1.83 to 11.20) after adjustments for *trans*-18:1 and risk factors such as diabetes, congestive heart failure, stroke, smoking status, education, and omega-3 fatty acid levels. An increase of *trans*-18:2 from 0.22% to 0.35% of total TFA levels corresponded with a 68% increase in risk (after adjustment for *trans*-18:1 and the risk factors mentioned above).

For participants with higher levels of *trans*-18:1, risk of fatal IHD events actually decreased. Risk estimates for increasing levels of *trans*-18:1 were as follows: 1.0 (reference); 0.29 (95% CI 0.14-0.61); 0.32 (95% CI 0.15-0.70); 0.45 (95% CI 0.21 to 0.97); 0.38 (95% CI 0.17 to 0.86) after adjustments for *trans*-18:2 levels and other risk factors listed previously. Levels exceeding the 20th percentile corresponded with a 66% lower risk (OR 0.34; 95% CI 0.18 to 0.63).

When the analysis was limited to participants who experienced sudden cardiac death, higher *trans*-18:2 levels were associated with higher risk and *trans*-18:1 levels were associated with lower risk of sudden cardiac death.

In summary, this study supports previous findings that higher levels of *trans*-18:2 FA in circulating RBC membranes increase the risk of fatal IHD, while higher levels of *trans*-18:1 TFA have the opposite effect on risk. These findings suggest that future dietary recommendations regarding TFA intake should differentiate between classes of TFA. These findings are especially significant in light of the current focus on eliminating all classes of TFA from the food supply. The authors emphasize that "although higher intake of [the] minor *trans* fatty acids appeared to increase risk, higher levels of the *trans* fatty acids commonly produced during partial hydrogenation ("*trans*-18:1") were associated with lower risks…" and advised that "future studies need to distinguish between *trans*-18:2 and *trans*-18:1 fatty acids to reassess the risks and possible benefits of different *trans* fatty acids." ∎

Lemaitre RN, King IB, Mozaffarian D, Sotoodehnia N, Rea TD, Kuller LH, Tracy R, Siscovick DS. Plasma phospholipid *trans* fatty acids, fatal ischemic heart disease, and sudden cardiac death in older adults: The Cardiovascular Health Study. *Circulation* 2006;114:209-215.

1979

Putting Dietary Cholesterol Guidelines to the Test

In the 1970s, dietary guidelines aimed at lowering serum cholesterol levels were similar to those we adhere to today. Most expert committees at the time recommended increasing linoleic acid intake (commonly found in vegetable oils), decreasing saturated fat consumption, and limiting dietary cholesterol to <300 mg per day. Because the evidence for a restriction in dietary cholesterol was largely inconsistent (due partly to discrepancies in study design) and because negative effects of dietary cholesterol could not be consistently demonstrated, Bronsgeest-Schoute et al. undertook a series of dietary trials to evaluate the effectiveness of these guidelines. The first and second trials addressed the effects of dietary cholesterol on serum cholesterol levels in linoleic acid (LA) rich and LA-poor diets, respectively. The third study assessed the consequences of removing eggs from the diets of individuals accustomed to high cholesterol intake.

In the first trial, Bronsgeest-Schoute et al. recruited 41 healthy volunteers between the ages of 19 and 35 for a cross-over study examining the effects of dietary cholesterol on serum cholesterol levels in individuals consuming LA-rich diets. The participants spent one week becoming accustomed to the experimental diet (14-15% energy from LA, mostly from soft margarine containing at least 60% LA, salad dressings, and other food oils), after which they were randomly assigned to one of two LA-rich dietary treatments of differing cholesterol content. The LA-rich high-cholesterol (HC) diet provided at least 600 mg of dietary cholesterol per day while the LA-rich low-cholesterol (LC) diet provided less than 200 mg. The cholesterol content of the HC diet was achieved by adding two egg yolks a day. The diets were designed to provide the same number of calories and similar macronutrient distributions. The participants followed these diets for two weeks, after which they switched to the alternate diet for another two-week period. Blood was drawn at the end of the first week and again following both diet treatment periods for assessment of serum lipids. Participants experienced an 11 ± 11 mg/dL (P<0.001) increase in serum total cholesterol levels between the LC (100 mg/day) and the HC (665 mg/day) diets.

Several predictive formulas had been developed by other researchers to predict the effects of dietary cholesterol on blood cholesterol levels. Based on most of these predictive formulas, an increase of 565 mg of cholesterol per day would result in an expected increase in serum total cholesterol of at least 28 mg/dL. Only one formula (Keys' equation), predicted a change of 11.8 mg/dL and came close to predicting the change observed in this population. The change in serum total cholesterol levels subsequent to short-term consumption of a cholesterol-rich diet was much lower than expected. These findings suggest that consuming a diet rich in LA blunts the effect of high cholesterol intake on serum cholesterol levels. The authors suggested that their findings demonstrate that the effects of cholesterol intake are nonlinear, meaning that there is probably a threshold beyond which additional cholesterol intake does not have as great an influence on serum cholesterol levels.

In the second study, Bronsgeest-Schoute et al. recruited 18 healthy volunteers to participate in a cross-over study to examine the effects of dietary cholesterol on serum lipids during consumption of a diet high in saturated fat and low in LA. Volunteers were randomly assigned to one of two treatment groups and were asked to complete two 3-week dietary treatment periods, one high in cholesterol and low in LA (HC), the other low in cholesterol and low in LA (LC). Both the HC and LC diets provided less than 5% of energy from LA, were high in saturated fat, and provided 35% of calories from fat. During the HC diet period, participants consumed 2 eggs per day in addition to other cholesterol-containing foods to achieve a cholesterol intake of at least 600 mg/day. The LC diet provided less than 200 mg of cholesterol per day. The diets were similar with regard to provision of total calories, carbohydrate, protein, alcohol, and LA. Following a period of 3 weeks on the first diet, the participants switched to the alternate diet and followed it for another period of 3 weeks.

Fasting blood samples were obtained at the end of each dietary period for measurement of serum lipids. Participants assigned to the HC diet consumed 731 mg cholesterol per day, on

average, while those assigned to the LC diet had a mean intake of 124 mg cholesterol per day. Overall, a difference of 600 mg cholesterol per day with high saturated fat intake resulted in an average change in serum cholesterol of 26 ± 20 mg/dL (P<0.01).

In summary, these findings suggest that consuming an additional 600 mg of cholesterol per day while consuming a high-saturated fat, low-LA, "normal" diet might increase serum cholesterol levels by ~26 mg/dL. The authors acknowledge that there was a difference in total fat intake between diet groups (HC: 36.3%, LC: 31.0%), which might have affected serum cholesterol levels. Further calculations led them to conclude that the contribution of cholesterol from ingested egg yolk was probably ~21 mg/dL. In light of the findings of the first and second diet trials by Bronsgeest-Schoute et al., it appears that the effects of dietary cholesterol on serum cholesterol levels are influenced by background diet. There appears to be a compound effect of consuming a diet high in saturated fat and high in cholesterol. In this study, the saturated fat seemed to potentiate the effects of dietary cholesterol, while in the previous study, the LA-rich diet appeared to blunt the effects of high cholesterol intake.

In the first two studies in this series, participants were in a semi-controlled feeding environment. For the third study, Bronsgeest-Schoute et al. utilized a less controlled free-living population. In a group of 44 volunteers, the research team undertook a short-term trial to determine the consequences of removing eggs from the diets of individuals who typically eat at least 7 eggs per week. These participants reported typically consuming an average of 742 mg cholesterol per day and 9.8 eggs per week prior to beginning the study. During the three-week study period, volunteers were not allowed to eat eggs or any product known to contain eggs, which brought their average cholesterol intake down to 262 mg cholesterol per day.

Blood cholesterol levels were assessed and recorded at the beginning and end of the experimental period. Overall, the removal of eggs and the decrease in cholesterol intake by an average of 478 mg per day resulted in a small, but statistically significant reduction in serum cholesterol levels (219 ± 40 mg/dL following the experimental period vs. 224 ± 39 mg/dL prior to the removal of eggs, a difference of 6 ± 17 mg/dL; P<0.05). Analyzing the groups by gender, however, no statistically significant difference was found between serum total cholesterol levels at baseline and following the removal of eggs from participants' diets. When the participants' total choles-

terol levels were analyzed based on baseline cholesterol levels, those who started out with total cholesterol levels <220 mg/dL showed a small, but statistically significant decrease (-7.2 ± 14.1; P<0.05) compared to those whose baseline levels were greater than 220 mg/dL (-4.9 ± 17.6; NS). Those who were not obese (32 of 44) also experienced significant decreases in serum total cholesterol levels (-9.0 ± 16.5; P<0.01) compared to those classified as obese (+1.6 ± 10.8 mg/dL; NS).

There was wide variation between individual responses to the removal of eggs from the diet. In fact, the distribution was apparently skewed by a small group of only 7 hyper-responders. These participants experienced decreases of 20-50 mg/dL after removing eggs from their diets (average decrease of 34 ± 10 mg/dL), a sizable drop from baseline compared to the average decrease of 1 ± 10 mg/dL experienced by the rest of the participants.

These findings demonstrated that a decrease of ~500 mg dietary cholesterol per day in those who are accustomed to eating upwards of 7 eggs per week resulted in an average decrease of 6 ± 16 mg/dL, a statistic that appeared to be heavily influenced by a small group of hyper-responders. Perhaps more importantly, this study provides evidence of the wide individual variation in response to dietary cholesterol, calling into question the suitability of a single dietary cholesterol intake guideline for the population as a whole. ■

Bronsgeest-Schoute DC, Hautvast JGAJ, and Hermus RJJ. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man: I. Effects of dietary cholesterol in a linoleic acid-rich diet. *Am J Clin Nutr* 1979; 33:2183-2187.

Bronsgeest-Schoute DC, Hermus RJJ, Dallinga-Thie GM, and Hautvast JGAJ. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man: II. Effects of dietary cholesterol in a linoleic acid-poor diet. *Am J Clin Nutr* 1979; 32:2188-2192.

Bronsgeest-Schoute DC, Hermus RJJ, Dallinga-Thie GM, and Hautvast JGAJ. Dependence of the effects of dietary cholesterol and experimental conditions on serum lipids in man: III. The effect on serum cholesterol of removal of eggs from the diet of free-living habitually egg-eating people. *Am J Clin Nutr* 1979; 32:2193-2197.

Timing of Maternal Undernutrition Associated with CAD Risk

Most health professionals are aware that adequate maternal intake of the B vitamin, folic acid, is critical to preventing birth defects that affect the development of the central nervous system. Because the days and weeks following conception are a critical period for fetal brain and spinal cord development, the timing of maternal intake of this nutrient is key. Health professionals also recognize that low birthweight stemming from inadequate maternal intake can increase the risk of respiratory complications for the newborn, decrease immune function, and impair cognitive development. However, fewer practitioners recognize the influence of maternal nutrition on the risk of adult-onset disease. Evidence suggests that inadequate maternal nutrition during critical periods of development can have lasting effects on specific organ systems, leaving offspring more susceptible to certain diseases of adulthood. Numerous studies have shown an association between slowed intrauterine growth and one of the most common adult conditions, coronary artery disease (CAD). However, the timing of the nutritional deprivation and the influence of such timing is not well understood. Data from the Dutch famine, a 5-month period of extreme food scarcity during World War II, gave researchers a unique opportunity to study the effects of acute maternal undernutrition during early, mid-, and late gestation on the incidence of CAD.

Researchers examined records from individuals born between November 1st, 1943 and February 28th, 1944, who were exposed to the famine prenatally. Famine exposure was defined as having experienced a period of >13 weeks of gestation during which the average adult's daily ration was <1000 kilocalories. Eligible parties were asked to participate in the study at ages 50 and 58 y.

Birth weight and socioeconomic status (SES) at birth were ascertained for each participant, and height, weight, BMI, blood pressure, glucose tolerance, and blood lipids were measured at ages 50 and/or 58 y. For the purposes of this study, any of the following signaled the onset of CAD: 1) angina pectoris; 2) Q waves on the ECG; 3) undergoing angioplasty or bypass surgery.

A total of 975 individuals participated in this study, 491 of whom participated at both follow-up time points (ages 50 and 58 y). Eighty-three participants had developed CAD by follow-up. Overall, compared to unexposed individuals, participants who were exposed to the famine during early, mid-, or late gestation had twice the risk of CAD. Those exposed to the famine during early gestation (conceived during the famine) displayed the highest CAD incidence (13%; hazard ratio (HR): 1.9). CAD incidence in those exposed during midgestation (8%; HR: 1.1) and late gestation (8%; HR: 0.8) were not significantly different from those not exposed to the famine. Individuals exposed during early gestation also developed CAD 3 years earlier, on average, than those not exposed.

Exposure to famine during any of the three gestational periods was associated with decreased glucose tolerance and an elevated ratio of LDL to HDL cholesterol. When these results were adjusted for maternal weight, age, number of pregnancies, and SES at birth, the association between famine exposure during early gestation and the incidence of CAD was only slightly attenuated (HR: 1.8). Birth weights were lower among participants with CAD than those without. Although this difference was not statistically significant, it lends support to the findings of previous studies.

Researchers have documented the negative effects of suboptimal nutrition during pregnancy on multiple CVD risk factors, including hypertension, glucose tolerance, and lipid metabolism. The results of the present study support these findings and add new information to this emerging body of research, providing data on the effects of undernutrition during specific gestational periods. These finding suggest that maternal nutrition during gestation, particularly during early gestation, may have a significant impact on CAD risk later in life. ■

Painter RC, de Rooij SR, Bossuyt PM, et al. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr* 2006; 84:322-7.

Genetic Polymorphism Modifies Responses to Dietary Cholesterol

It is widely recognized that high intakes of saturated fat and certain *trans*-fatty acids (TFAs) are dietary factors that can increase the risk of heart disease. Additionally, current guidelines recommend that individuals limit their daily intake of dietary cholesterol. We know, however, that individual responses to changes in fat and cholesterol intake are highly variable. Although there is limited evidence to explain these differences, researchers have identified certain genetic polymorphisms—many of which are responsible for the expression of key proteins in cholesterol metabolism—that may be responsible for some of the variation in response to cholesterol intake. It is thought that the expression of ATP-binding cassette transporters (which facilitate the transport of lipids across cell membranes) modifies cholesterol absorption in the small intestine. A recent study by Herron et al. demonstrated the influence of ATP-binding cassette G5 (ABCG5) polymorphisms on individual plasma lipid responses to a cholesterol feeding challenge.

Forty men and 51 premenopausal women were recruited to participate in this randomized crossover study. Each was randomly assigned to follow a high-cholesterol (EGG) or placebo (SUB) diet for a period of 30 days. Following a 3-week washout period, participants switched to the alternate dietary regimen for a second treat-

ment period of 30 days. Throughout the study, all participants were asked to follow a self-selected diet consistent with NCEP Step I guidelines. When following the EGG diet protocol, participants were expected to consume the liquid equivalent of 3 whole eggs, which provided an additional 640 mg cholesterol and 600 µg lutein and zeaxanthin (combined) per day. While following the SUB diet protocol, participants were expected to consume an equivalent weight of a fat-free, cholesterol-free egg substitute which provided no additional cholesterol, lutein, or zeaxanthin.

Two fasting blood samples were obtained from each participant at the beginning of the study and following each 30-day treatment period for measurement of plasma total, LDL-, and HDL-cholesterol levels (as well as plasma carotenoid levels in a subset of the study group). At baseline and following each treatment period, weight, blood pressure, activity level, smoking status, and alcohol intake were also recorded to assess their influence on study results.

The participants reported compliance with NCEP Step I dietary guidelines throughout both treatment periods and participants' body weights did not change significantly over the course of the study. Intakes of total, saturated, monounsaturated, and polyunsaturated fats and cholesterol were higher during the EGG period than during the SUB period for all participants.

Total and LDL-cholesterol levels for participants with the C/C genotype were higher following the EGG protocol than at the end of the SUB protocol (EGG 182.6 ± 32.7 mg/dL vs. SUB 168.9 ±

27.6 mg/dL for total cholesterol; EGG 105.0 ± 29.5 mg/dL vs SUB 93.8 ± 24.4 mg/dL for LDL cholesterol; P<0.05 for both measures). Neither total cholesterol, nor LDL cholesterol levels differed following the EGG and SUB periods for participants with the C/G and G/G genotypes. Those with the C/C genotype also had higher total and LDL cholesterol levels following the EGG protocol than did those with the C/G and G/G genotypes. Neither baseline total cholesterol levels, nor gender were found to be significant predictors of the changes in plasma total cholesterol concentrations, indicating that the observed differences were diet-induced. With regard to plasma carotenoids, combined lutein and zeaxanthin levels rose by 36% in those with the C/C allele, whereas in those with C/G or G/G polymorphisms, it rose by 23%.

The population sample for this study was small, however, the results of this trial warrant further research and suggest that ABCG5 polymorphisms do have an effect on individual plasma lipid responses to dietary cholesterol. Although the scientific community recognizes that there is wide variation in individual responses to changes in dietary fat and cholesterol intake, only generalized nutrition recommendations are available at this time for individuals concerned with reducing their risk for coronary heart disease (CHD). Given that heart disease is the leading cause of death for both men and women in the US and Canada, fine-tuning individual dietary recommendations to reduce the risk of atherosclerosis and CHD is not only relevant, but critical for progress in this area. ■

Herron KL, McGrane MM, Waters D, et al. The ABCG5 polymorphism contributes to individual responses to dietary cholesterol and carotenoids in eggs. *J Nutr* 2006; 136:1161-1165.

EDITORIAL

Now it Starts to Make Sense

One of the consistent arguments for having a dietary cholesterol restriction is that some people are hyper-responders to dietary cholesterol and there is no easy test to detect who these people are (see review of studies by Bronsgeest-Schoute et al.). Over the years there have been many reports of genetic polymorphisms of apo E, apo B and apo A-IV related to an increased sensitivity to dietary cholesterol, but for the most part these polymorphisms couldn't explain why 15-20% of the population had a higher than expected plasma cholesterol response to a dietary cholesterol challenge. Now the report by Robinson et al., reviewed in this issue of *Nutrition Close-Up*, sheds some much needed light on the issue.

First, however, it is important to put the hypo-responder/hyper-responder question in some quantitative context. Many people think a hyper-responder has this massive plasma cholesterol response to cholesterol intake, and therefore needs to avoid all sources of dietary cholesterol. In fact, the responses of both hypo- and hyper-responders, while statistically different, are fairly modest. The average plasma cholesterol response of a hypo-responder is 1.4 mg/dL per 100 mg/day cholesterol compared to hyper-responders at 3.9 mg/dL per 100 mg/day cholesterol. And while most of this differential response occurs in the LDL fraction (see table), studies by Fernandez and colleagues (reviewed in previous issues of *Nutrition Close-Up*) have shown that the increase is in the large, buoyant LDL fraction and not in the highly atherogenic small, dense LDL subfraction.

	Δ mg/dL per 100 mg/day cholesterol		
	Total	LDL	HDL
Hypo-responders	1.4	0.8	0.5
Hyper-responders	3.9	2.8	0.7

And now emerging evidence indicates that fetal programming plays a role in determining the extent of response to dietary cholesterol as well as overall response to dietary interventions and CHD risk. Not only is there epidemiological evidence for this phenomenon, but there is also an animal model for the observation. Finally, a little clarity on a problem that has vexed cholesterol researchers for the past 25 years. It was never clear why some people could get away with a diet high in saturated fat and not have elevated plasma cholesterol levels while others appeared hyper-sensitive to the LDL raising effects of saturated fat. So much for saying it must be in your genes!

The beauty of fetal programming, as described by Dr. David Barker (of the "Barker Hypothesis"), is that it facilitates rapid metabolic adaptations in the fetus to increase survival potential in its new environment, either nutrient rich or nutrient poor. The benefit is a faster and more flexible response to environmental factors than can be achieved through evolutionary genetic adaptations. No doubt in some ethnic groups both genetic and fetal programming play a role in determining the plasma cholesterol response to dietary lipids (the health problems encountered by hunter-gather groups suddenly exposed to calorie-rich food supplies for example).

Two factors become important in considering the impact of fetal programming on CVD risk. The first is obvious. Good nutrition during fetal development is an important part of CVD risk reduction and needs to be a priority. Making sure mothers-to-be are getting sufficient high-quality protein, choline, and other essential nutrients could have a major impact on the health of their adult children. (Eggs can play a major role in facilitating optimal fetal development especially in developing countries and for low socioeconomic populations.) Second, maybe the perceived epidemic of heart disease in developing countries isn't just a function of the adaptation of western lifestyles, and the always-condemned fast food chains, but also a function of poor nutrition in the 1940s resulting in low birth weight infants exhibiting their higher risk profile sixty some years later. An individual's CVD risk appears to be the sum of a combination of factors: genetic profile, fetal programming, and present lifestyle. No wonder there is so much heterogeneity of response to dietary factors in the population…one diet has a hard time fitting all.

I wonder, given the evidence we have today, as compared to forty years ago, if an extensive analysis of the data in its totality (not just the past five years) would result in the same set of dietary recommendations we have lived with for forty years. Wouldn't it be fun to find out! ◼

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NUTRITION CLOSE-UP

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