The response of lipoproteins to dietary fat and cholesterol is higher in lean than in obese persons – a review

Current Atherosclerosis Reports 2005, 7:460–465

Martijn B. Katan Ph.D.

Wageningen Centre for Food Sciences
and
Division of Human Nutrition
Wageningen University
Bomenweg 2
6703 HD Wageningen
The Netherlands
Fax : +31 317 485369
E-mail : wcfs1@wur.nl

Correspondence as of September 2008:
Prof dr Martijn B. Katan
VU University
Institute of Health Sciences
De Boelelaan 1085
1081 HV Amsterdam
The Netherlands
Tel : +31 20 598 2610
E-mail : katan99@falw.vu.nl

Abbreviations

BMI Body Mass Index

HDL High Density Lipoproteins

LDL Low Density Lipoproteins

Abstract

Individuals differ in the response of their blood lipoproteins to cholesterol-lowering diets. One characteristic clearly associated with susceptibility to diet is leanness: many studies show that total, LDL and HDL cholesterol concentrations respond more strongly to dietary fat and cholesterol in lean than in obese subjects. This is unlikely to be due differences in dietary compliance. A metabolic explanation is that obese people have a higher rate of total body cholesterol synthesis. The LDL receptors in their liver cells are partly suppressed by this large stream of endogenous cholesterol coming in from their enterohepatic circulation, and the amount added by dietary cholesterol relative to the endogenous pool would be less than in lean people.

Whatever the mechanism, diets low in saturated fat and cholesterol are less effective in the obese; the most effective way for them to normalize their blood lipids is to lose weight, which is, unfortunately, hard to achieve in our society.

Introduction

Dietary recommendations are more effective when they are tailored to an individual's needs. Indeed, the idea that "One size doesn't fit all" forms the basis of the new US food pyramid [1]. MyPyramid [1] focuses on individual caloric needs because obesity is now the major nutritional problem in the US. However, attempts at personalization of dietary recommendations to lower cholesterol were already made over 50 years ago. In 1952 Groen wrote: "some individual or 'constitutional' peculiarity determines or modifies the reaction of each subject's serum cholesterol to the diet" [2]. In dietary trials of long duration, Ahrens et al [3] and Connor and Connor [4] also observed differences between subjects in the response of serum cholesterol to diet. Identification of the "constitutional peculiarities" that determine these differences would make dietary prevention and treatment of dyslipidemia more effective – people would be persuaded more easily to follow a diet if they felt that it was tailored to their personal needs rather than based on a statistical average of a large number of strangers.

Developments in genomics have made such personalized diets seem nearer [5], but in practice results have been disappointing: the replicability of genetic associations is poor [6], and as a result journals are putting restrictions on publication of such studies [7]. The diet-and-lipid field is no exception: associations between individual genotypes or single nucleotide polymorphisms and response of blood lipoproteins to diet have usually not been reproducible [8]. Thus the genomic revolution has not yet brought us any nearer to individually tailored cholesterol-lowering diets [9].

However, there is still hope for personal diets. There is one trait that has been consistently associated with the response of serum cholesterol to diet, and that is body fatness, or rather leanness. Here I review this association and its implications for clinical practice.

Effect of dietary fat and cholesterol on lipoproteins

The major dietary determinant of blood lipoproteins is fat intake. Not all fats raise cholesterol; only saturated and trans fatty acids do that, while omega-6 polyunsaturated fatty acids from vegetable oils actually decrease cholesterol concentrations[10]. Diets high in such polyunsaturated fatty acids also lower the ratio of total to HDL cholesterol [10], and they lowered coronary heart disease in controlled clinical trials [11].

The concept of hypo- and hyperresponsiveness of blood lipids to diet is mostly connected with studies of dietary cholesterol, even though the effect of dietary cholesterol on blood lipoproteins is less than that of dietary fatty acids. It has been questioned whether reduction of cholesterol intake reduces the risk of coronary heart disease at all. Dietary cholesterol, usually given in the form of egg yolk, does cause massive hypercholesterolemia and atherosclerosis in rabbits and other animals [12], and an analysis of 4 prospective epidemiological studies [13] suggested that in man there was also an increase in the risk of coronary heart disease associated with a higher dietary cholesterol intake; the increase was even larger than that predicted by the effect on serum cholesterol alone. On the other hand, there are no controlled clinical trials of the effect of egg yolk cholesterol on coronary heart disease, and the effect on serum cholesterol is much less in humans than in animals such as rabbits. Still, dietary cholesterol does raise serum cholesterol in humans in properly designed trials. Both LDL and HDL cholesterol are increased but in general LDL is more affected, and as a result the ratio of total or LDL cholesterol to HDL cholesterol goes up when intake of cholesterol is increased [14].

From early on, investigators were struck by the wide range of responses of different individuals to the same amount of dietary cholesterol [15;16], and there have been many attempts to find characteristics that predict the response of an individuals serum cholesterol to dietary cholesterol. Before we contemplate these characteristics we will first consider to what extent the observed range of responses represents a biological reality.

Individual responsiveness is partly a statistical artifact

When the same stimulus elicits a wide range of responses in different people it is tempting to ascribe this variation to innate differences between the subjects. But if subjects truly differ in responsiveness then these differences should be reproducible. The limited data on subjects studied repeatedly on the same diets suggest that differences in response are poorly reproducible. The idea that some humans are insensitive to dietary cholesterol received a boost from a study of Bronsgeest-Schoute et al [17], who observed a very variable response when eggs were removed from the habitual egg-rich diet in volunteers. However, when we repeated this trial 6 years later in the same volunteers with the same challenge and design [18], the correlation between an individual's response in the first and in the second study was only $r = 0.32$: many of the putative hyperresponders had become hyporesponders, and vice versa. The same was true for other cohorts of volunteers whom we tested repeatedly over the years [19-22]. Keys and coworkers [23], who studied one group of men on a variety of diets, also concluded that true non-responsiveness is rare if it exists at all, even though one subject may react aberrantly in one particular trial.

The explanation for this lack of consistency from one trial to another is simple: like all biological attributes, cholesterol levels in an individual fluctuate, and changes in cholesterol level from one diet to another fluctuate even more. This seemingly trivial fact implies that different patients will show different responses to treatment not because of inherent metabolic differences but because of random fluctuations. If the "hyperresponders" are retested many of them will turn out to be 'hyporesponders' the second time, and vice versa. Figure 1 illustrates this for cholesterol-lowering diets, but the same holds for any measurement that is subject to biological variability.

==========Figure 1 about here ==========

Teasing out consistent responses from random variation has proved to be hard almost to the point of being impossible. What makes studies of individual responses so difficult is that a change in a level is much more sensitive to random noise than the level itself. For instance, serum cholesterol varies within a subject with a coefficient of variation of about 7% [24;25] but the response of serum cholesterol to diet when measured repeatedly within the same subject shows a coefficient of variation of about 74% [21]. There are two reasons for this. First, the response is a difference between two measurements each of which is subject to random noise, and the noise thus adds up. More importantly, any change of level in response to treatment is much smaller than the level itself. For example, a within-subject standard deviation of serum cholesterol of 0.42 mmol/L represents a coefficient of variation of 7% around the mean level of 6 mmol/L. However, a typical response to a fat-modified diet is a fall of 0.6 mmol/L, and here a standard deviation of 0.42 mmol/L represents a coefficient of variation of 70%. Therefore a given subject may easily show a response of 1.2 mmol/L in one experiment and of 0 in the next experiment, and associations of responses with e.g. genetic polymorphisms become largely a matter of chance.

Body fatness and the response of serum cholesterol to diet

The statistical considerations given above explain why spurious correlations of single-nucleotide polymorphisms (SNP's) with the response of blood lipids to diet are so frequent. However, there are some characteristics that do associate reliably with response, and the characteristic associated most consistently with the response of blood lipoproteins to diet is body fatness. Bronsgeest-Schoute [17] already reported a significant negative correlation between changes in serum cholesterol levels and the Body Mass Index (BMI; weight divided by height squared) when dietary cholesterol intake was reduced. Thus thin people showed a larger fall when cholesterol was removed from their diets than fat people. This association has been seen in many trials since then. Table 1 gives an overview of dietary trials that reported on the relation between body mass index and response of lipoproteins to diet. The table is not exhaustive but the number of trials that reported a reduced sensitivity of obese people to changes in diet is remarkable. The studies of Cole [26] and Jansen [27] were expressly designed to test the hypothesis that fatness attenuates response, and both found that the response in larger subjects was indeed less than half of that in thinner people (table 1). The effect was not statistically significant in all studies, but that is explained by the problem of noise discussed above. None of the studies reported an effect in the opposite direction: if there was a difference then

susceptibility always went down with increasing body fatness. This was not just seen in subjects with pathologic obesity but also in comparisons of thin people with those of average weight, and it was observed in metabolic ward studies where all food was provided and food intake was carefully monitored both by supervision and by the use of biological markers of intake. This makes it less likely that the phenomenon is due to poor adherence on the part of overweight participants, and it suggests a metabolic explanation.

The effect is not limited to dietary cholesterol: there is a congruence between the response to dietary cholesterol and to dietary fatty acids [28], and lean people are more responsive to both dietary cholesterol and to saturated fatty acids [26;27;29-31]. The increased responsiveness is seen for both HDL and LDL cholesterol, and it is seen in men and women (in spite of isolated reports to the contrary) and in adults and children [31]. The effect extends beyond blood lipids to coronary heart disease mortality: Goff et al observed that in the Chicago Western Electric cohort, cholesterol intake at baseline was associated with 25-year mortality from coronary heart disease in lean but not in overweight men. Fatter men apparently did not benefit from a diet lower in cholesterol [32].

Neither this cohort study nor the dietary trials can tell us definitively whether BMI is the causal factor here. The subjects in the trials were not randomized to various degrees of body fatness, and therefore the association between BMI and response observed in the trials is an ‘epidemiological’ (i.e. observational) association only. Therefore BMI could act as a surrogate for some other characteristic that really determines susceptibility to diet. The fact that BMI remained a significant predictor of response after multivariate adjustment in several studies [29;31;33-35] reduces but does not eliminate the chance that it is a surrogate for some other characteristic. However, it is indisputable that there is something in the physiology or the behavior of overweight people that attenuates their response to cholesterol-lowering diets.

Mechanisms

In spite of 40 years of research, the mechanisms that mediate the effects of fatty acid saturation on lipoprotein levels have not been clarified [36-38], and that makes it difficult to speculate why obese subjects would be less responsive to dietary fat quality than lean subjects. In contrast, the pathway from dietary cholesterol to plasma LDL is clear [39]: dietary cholesterol adds to the cholesterol that goes from the gut to the liver where it suppresses expression of the LDL receptor in hepatocytes. As a result, clearance of LDL from plasma is decreased and plasma LDL rises until a new steady state has been established. This offers an explanation why obese people would be less responsive to dietary cholesterol: the obese have a higher rate of total body cholesterol synthesis and a larger pool of cholesterol circulating from the gall bladder to the gut and back to the liver [40]. This large amount of cholesterol that continuously arrives in the liver would suppress the LDL receptor and cause higher plasma LDL levels, which are indeed seen in the obese. Their response to dietary cholesterol would be lower because the amount taken in with the diet would be small compared with the large amount already present in the enterohepatic cholesterol pool, and it would therefore not contribute to further suppression of the LDL receptor. [Grundy SM, personal communication 1985]

Conclusions

Obese people are at increased risk of cardiovascular disease. However, diets low in saturated fat and cholesterol are less effective in the obese than in lean people, possibly because the LDL receptors in their liver cells are suppressed by the large stream of endogenous cholesterol in their enterohepatic circulation. The most effective way for the obese to normalize their blood lipids is to lose weight [41;42]. Unfortunately we have created a society which makes such weight loss very hard to attain.

Acknowledgments

I thank Dr Scott Grundy for sharing his insights.

Our studies on diet and response were supported by the Netherlands Heart Foundation. M.B. Katan is supported by the Wageningen Centre for Food Sciences (WCFS), an alliance of six industrial partners (AVEBE, Cosun, CSM, DSM, Unilever, and NZO) and four research organizations (Wageningen University and Research Centre, Maastricht University, NIZO Food Research, and TNO Quality of Life) with financial support from the Dutch Ministry of Economic Affairs.

Reference List

1. US Dept of Agriculture. Steps to a Healthier You. www.mypyramid.gov . visited 6 July 2005.

2. Groen JJ, Tjiong BK, Kamminga CE, Willebrands AF: **The influence of nutrition, individuality and some other factors including various forms of stress, on the serum cholesterol : an experiment of nine months duration in 60 normal human volunteers**. *Voeding* (the Netherlands) 1952, **13:**556-587.

3. Ahrens EH, Hirsch J, Insull W, Tsaltas TT, Blomstrand R, Peterson ML: **The influence of dietary fats on serum-lipid levels in man**. *Lancet* 1957, **1:**943-953.

4. Connor WE, Connor SL: **The key role of nutritional factors in the prevention of coronary heart disease**. *Prev Med* 1972, **1:**49-83.

5. DeBusk RM, Fogarty CP, Ordovas JM, Kornman KS: **Nutritional genomics in practice: where do we begin?** *J Am Diet.Assoc.* 2005, **105:**589-598.

6. Ioannidis JP, Ntzani EE, Trikalinos TA, Contopoulos-Ioannidis DG: **Replication validity of genetic association studies**. *Nat.Genet.* 2001, **29:**306-309.

7. Rebbeck TR, Martinez ME, Sellers TA, Shields PG, Wild CP, Potter JD: **Genetic variation and cancer: improving the environment for publication of association studies**. *Cancer Epidemiol.Biomarkers Prev.* 2004, **13:**1985-1986.

8. Weggemans RM, Zock PL, Meyboom S, Funke H, Katan MB: **Apolipoprotein A4-1/2 polymorphism and response of serum lipids to dietary cholesterol in humans**. *JLR* 2000, **41:**1623-1628.

9. Masson LF, McNeill G: **The effect of genetic variation on the lipid response to dietary change: recent findings**. *Curr.Opin.Lipidol.* 2005, **16:**61-67.

10. Mensink RP, Zock PL, Kester ADM, Katan MB: **Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am.J.Clin.Nutr.* 2003, **77:**1146-1155.

The definitive study on the effect of dietary fatty acids and carbohydrates on blood lipoproteins in humans.

11. Sacks FM: **Dietary fats and coronary heart disease. Overview**. *J Cardiovasc Risk* 1994, **1:**3-8.

12. Connor WE, Connor SL: **Dietary cholesterol and coronary heart disease**. *Curr.Atheroscler.Rep.* 2002, **4:**425-432.

13. Stamler JS, Shekelle RB: **Dietary cholesterol and human coronary heart disease**. *Arch Pathol Lab Med* 1988, **112:**1032-1040.

14. Weggemans RM, Zock PL, Katan MB: **Dietary cholesterol from eggs increases the ratio of total cholesterol to high- density lipoprotein cholesterol in humans: a meta-analysis**. *Am.J.Clin.Nutr.* 2001, **73:**885-891.

15. Mjassnikow AL: **Ueber alimentaere Beeiunflussung der Cholesterinaemie beim Menschen**. *Z f klin Medizin* 1926, **103:**767-778.

16. Okey R, Stewart D: **Diet and blood cholesterol in normal women**. *J Biol Chem* 1933, **99:**717-727.

17. Bronsgeest-Schoute HC, Hermus RJJ, Dallinga-Thie GM, 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.

18. Beynen AC, Katan MB: **Reproducibility of the variations between humans in the response of serum cholesterol to cessation of egg consumption**. *Atherosclerosis* 1985, **57:**19-31.

19. Katan MB, Beynen AC: **Hyper-response to dietary cholesterol in man**. *Lancet* 1983, **1:**1213.

20. Katan MB, Beynen AC, De Vries JHM, Nobels AP: **Existence of consistent hypo- and hyperresponders to dietary cholesterol in man**. *Am J Epidemiol* 1986, **123:**221-234.

21. Katan MB, Van Gastel AC, De Rover C, Van Montfort MAJ, Knuiman JT: **Differences in individual responsiveness of serum cholesterol to fat-modified diets in man**. *Eur J Clin Invest* 1988, **18:**644-647.

22. Beynen AC, Katan MB, Van Zutphen LFM: **Hypo- and hyperresponders: individual differences in the response of serum cholesterol concentration to changes in diet**. *Adv Lipid Res* 1987, **22:**115-171.

23. Jacobs DR, Anderson JT, Hannan P, Keys A, Blackburn H: **Variability in individual serum cholesterol response to change in diet**. *Arteriosclerosis* 1983, **3:**349-356.

24. Harris EK, Kanofsky P, Shakarji G, Cotlove E: **Biological and analytic components of variation in long-term studies of serum consistuents in normal subjects**. *Clin Chem* 1970, **16:**1022-1027.

25. Jacobs DR, Barrett-Connor E: **Retest reliability of plasma cholesterol and triglyceride : the lipid research clinics prevalence study**. *Am J Epidemiol* 1982, **116:**878-885.

26. Cole TG, Bowen PE, Schmeisser D, Prewitt TE, Aye P, Langenberg P, Dolecek TA, Brace LD, Kamath S: **Differential reduction of plasma**

cholesterol by the American Heart Association Phase 3 Diet in moderately hypercholesterolemic, premenopausal women with different body mass indexes. *Am.J.Clin.Nutr.* 1992, **55:**385-394.

27. Jansen S, Lopez-Miranda J, Salas J, Castro P, Paniagua JA, Lopez-Segura F, Ordovas JM, Jiménez-Perepérez J, Blanco A, Perez Jimenes F: **Plasma Lipid Response to Hypolipidemic Diets in Young Healthy Non-Obese Men varies with Body Mass Index. *J Nutr* 1998, **128:**1144-1149.

One of the studies that directly tested the hypothesis of an interaction between Body Mass Index and responsiveness

28. Katan MB, Berns MAM, Glatz JFC, Knuiman JT, Nobels AP, De Vries JHM: **Congruence of individual responsiveness to dietary cholesterol and to saturated fat in man**. *JLR* 1988, **29:**883-892.

29. Cox C, Mann J, Sutherland W, Ball M: **Individual variation in plasma cholesterol response to dietary saturated fat**. *BMJ* 1995, **311:**1260-1264.

30. Hannah JS, Jablonski KA, Howard BV: **The relationship between weight and response to cholesterol-lowering diets in women**. *Int J Obes.Relat Metab Disord.* 1997, **21:**445-450.

*31. Denke MA, Adams-Huet B, Nguyen AT: **Individual cholesterol variation in response to a margarine- or butter-based diet: A study in families**. *JAMA* 2000, **284:**2740-2747.

A valuable field study of the effect of dietary fat on lipoproteins. Shows attenuating effect of overweight on the response to diet in both adults and children

32. Goff DC, Shekelle RB, Katan MB, Gotto AM, Stamler JS: **Does Body Fatness Modify the Association Between Dietary Cholesterol and Risk of Coronary Death ? Results from the Chicago Western Electric Study**. *Arterioscler Thromb* 1992, **12:**755-761.

33. Clifton PM, Abbey M, Noakes M, Beltrame S, Rumbelow N, Nestel PJ: **Body fat distribution is a determinant of the high-density lipoprotein response to dietary fat and cholesterol in women**. *Arterioscler.Thromb.Vasc.Biol.* 1995, **15:**1070-1078.

34. Katan MB, Beynen AC: **Characteristics of human hypo- and hyperresponders to dietary cholesterol**. *Am J Epidemiol* 1987, **125:**387-399.

35. Goff DC, Shekelle RB, Moyé LA, Katan MB, Gotto AM, Stamler JS: **Does Body Fatness Modify the Effect of Dietary Cholesterol on Serum Cholesterol? Results from the Chicago Western Electric Study**. *Am J Epidemiol* 1993, **137:**171-177.

36. Spritz N, Ahrens EH, Grundy SM: **Sterol balance in man as plasma cholesterol concentrations are altered by exchanges of dietary fats**. *J Clin Invest* 1965, **44:**1482-1493.

37. Spady DK, Dietschy JM: **Dietary saturated triacylglycerols suppress hepatic low density lipoprotein receptor activity in the hamster**. *Proc Natl Acad Sci* 1985, **82:**4526-4530.

38. Lin J, Yang R, Tarr PT, Wu PH, Handschin C, Li S, Yang W, Pei L, Uldry M, Tontonoz P, Newgard CB, Spiegelman BM: **Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP**. *Cell* 2005, **120:**261-273.

39. Brown MS, Goldstein JL: **A receptor - mediated pathway for cholesterol homeostatis**. *Science* 1986, **232:**34-47.

40. Bennion LJ, Grundy SM: **Effects of obesity and caloric intake on biliary lipid metabolism in man**. *J Clin Invest* 1975, **56:**996.

41. Leenen R, Kooy van der K, Meyboom S, Seidell JC, Deurenberg P, Weststrate JA: **Relative effects of weight loss and dietary fat modification on serum lipid levels in the dietary treatment of obesity**. *JLR* 1993, **34:**2183-2191.

42. Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ: **Short-term consumption of a low-fat diet beneficially affects plasma lipid concentrations only when accompanied by weight loss. Hypercholesterolemia, low-fat diet, and plasma lipids**. *Arterioscler.Thromb.* 1994, **14:**1751-1760.

43. Oh SY, Miller LT: **Effect of dietary egg on variability of plasma cholesterol levels and lipoprotein cholesterol**. *Am.J.Clin.Nutr.* 1985, **42:**421-431.

44. Knopp RH, Retzlaff B, Fish B, Walden CE, Anderson M, Aikaw K, Kahn SE. Effects of insulin resistance and obesity on lipoproteins and sensitivity to egg feeding and fat restricted diet. International Atherosclerosis Society E-newsletter, January 2004 www.athero.org/comm-index3b.asp. 2005. 5-7-2005.

Ref Type: Electronic Citation

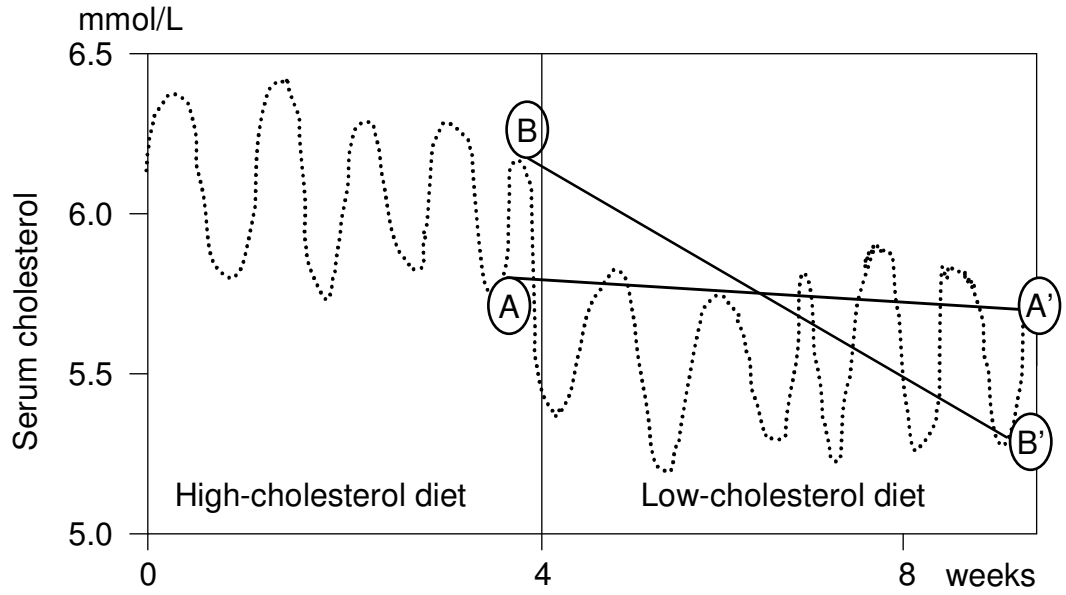
Table 1. Relation of body mass index (BMI) at baseline with the response of serum cholesterol to dietary cholesterol and fat in dietary experiments

Reference	**Year**	**Dietary intervention**	**Relation of BMI with absolute change in serum cholesterol**	**Direction of effect**	**Remarks**
Bronsgeest-Schoute [17]`	1979	Removal of eggs	r= -0.32 between BMI and response of serum cholesterol	↓	r = 0.06 when 33 subjects were retested [18]
Oh [43]	1985	Addition of eggs	Hyperresponders had mean BMI of 24.7 kg/m^2, and hyporesponders had mean BMI of 26.1 kg/m^2,	↓	P > 0.05
Katan [34]	1987	Addition of egg cholesterol	r = -0.50 between BMI and response of serum cholesterol	↓	
Cole [26]	1992	Low-fat diet	Response of serum cholesterol was -0.51 mmol/L in women with BMI < 24, and -0.20 mmol/L in women with BMI >30	↓	Study explicitly designed to test effect of BMI on response
Goff [35]	1993	Observational cohort study, not an experiment	Change in serum cholesterol in first year was associated with change in cholesterol intake for men with BMI	↓	25-year coronary mortality in this cohort correlated with cholesterol intake in lean men but not in fat men [32]

			< 24.2 but not for men with BMI > 26.6		
Clifton [33]	1995	Addition of milk fat plus egg yolk	Response of HDL was inversely correlated with BMI or waist-hip ratio	(↓)	No relation with LDL cholesterol
Cox [29]	1995	Saturated vs. polyunsaturated fat	Hyperresponders had mean BMI of 25 kg/m^2, and hyporesponders had mean BMI of 26 kg/m^2	(↓)	P = 0.82
Hannah [30]	1997	15 vs. 10% saturated fat	r = -0.33 between BMI and response of serum cholesterol in women, and r = -0.07 in men	↓	P = 0.03 in women and P > 0.05 in men
Jansen[27]	1998	Saturated fat vs. NCEP-1 diet	Response of serum cholesterol was -16% in men with BMI <25, and -7% in men with BMI 25-30	↓	Study explicitly designed to test effect of BMI on response
Denke [31]	2000	Margarine vs butter	Response of LDL cholesterol was -0.34 mmol/L in subjects with BMI < 21, and -0.23 mmol/L in subjects with BMI ≥ 30	↓	P = 0.008 in children, P = 0.01 in adults
Knopp [44]	2004	Addition of eggs	Response of serum cholesterol was higher in men with BMI <27.5 than in men with BMI	↓	<aanvullen vanuit unpublished metabolic syndrome>

			>27.5		

1 mmol/L = 38.7 mg/dL



Legend to figure

Figure 1. How random fluctuations give rise to apparent hyper- and hyporesponsiveness.
The dotted line represents a continuous registration of serum cholesterol values in a patient when switched from a high- to a low-cholesterol diet. The curve is fictitious, but it is based on the known coefficient of variation of cholesterol within subjects, and on the lifetime of LDL particles which is about 3 days. If blood samples had been taken at points AA', the response to the diet would have seemed to be 0.1 mmol/L. If on another occasion – or in a twin of this subject – blood had been collected at points BB' the apparent response to the same diet would have been 1 mmol/L.