Item: BMJ-UK; Article ID: beinortast2904;
Article Type: Letter; TOC Heading: Letters; DOI: 10.1136/bmj.j2108

Revisiting the diet-heart hypothesis

Revisiting the diet-heart hypothesis: critical appraisal of the Minnesota Coronary Experiment

Tumas Beinortas,[1] physician and researcher, Kamal R Mahtani,[2] deputy director, David Nunan,[2] departmental lecturer and senior research fellow

[1]St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK

[2]Centre for Evidence Based Medicine, Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

tumasbeinortas@gmail.com

Several articles have concluded that associations between high cholesterol and premature death are lacking and advocate for revision of current guidance advising low consumption (<10%) of saturated fat.[1-3] Ramsden and colleagues recovered 45 year old data from the Minnesota Coronary Experiment, a randomised controlled trial conducted in state mental hospitals and nursing homes in Minnesota, USA, and reassessed the effect of a diet rich in linoleic acid on serum cholesterol and mortality.[3] The authors found that the diet lowered total cholesterol but did not reduce the risk of premature mortality and might even have increased it.

To change current consensus, however, these claims should be based on valid and reliable evidence. We performed a critical appraisal of the Minnesota Coronary Experiment using the methods and data provided in three publicly available descriptions of this trial: two peer reviewed papers (by Ramsden and colleagues[3] and Frantz et al[4]) and a thesis by Broste,[5] on which the primary data in the analysis by Ramsden and colleagues were based.

We used the Cochrane risk of bias tool to assess the internal validity of data from the original experiment (table 1).[6]

Table 1 Cochrane risk of bias table

Entry	Judgment	Support for judgment
Selection bias (random sequence generation)	Unclear risk of bias	Participants were randomised using 512 cells and eight criteria. But the method used to generate the random sequence or how it was implemented are not discussed
Selection bias (allocation concealment)	Unclear risk of bias	Allocation concealment or allocation implementation are not described
Performance bias (blinding of participants and personnel)	Low risk of bias	Used computer generated code cards uninterruptable to participants Participants were allowed to try different diets before enrolment

Blinding of outcome assessment (detection bias for all cause mortality)	Low risk of bias	Objective outcome, less susceptible to detection bias
Blinding of outcome assessment (detection bias for other outcomes)	Unclear risk of bias	At time of study, serum cholesterol would have been recorded manually, making it a semi-objective. As outcome assessors were not blinded this represents an increased risk of bias
Incomplete outcome data (attrition bias) (long term >6 weeks)	High risk of bias	75% attrition in the first year ~30% annual attrition in later years More participants lost from control group Only per protocol analysis was performed
Selective reporting (reporting bias)	High risk of bias	Authors focused on mortality and serum cholesterol—outcomes that achieved statistical significance in MCE Outcomes that did not achieve statistical significance or offered contradicting results were not explicitly reported

MCE=Minnesota Coronary Experiment

We identified several factors that weaken the validity of conclusions drawn from the experiment. Here we focus on the areas of most concern—discrepancies in data and selective outcome reporting, high attrition, and lack of wider relevance.

Discrepancies in data and selective outcome reporting

The total number of participants and event rates differed in each report of the same data: 9570 participants and 517 deaths in Ramsden and colleagues, 9057 and 517 in Frantz et al, and 9570 and 477 in Broste's thesis. The difference in event rates between intervention and control groups was driven by events occurring in those aged >65 years.[5] We found a discrepancy in the numbers analysed for this age group too: 626 participants were left after the first year in Broste's thesis, whereas Ramsden and colleagues report only 595. These inconsistencies cast doubt over the overall precision of data collection and its recovery.

Ramsden and colleagues focused on one statistically significant association with mortality—that of serum cholesterol concentrations. But smoking, a higher body mass index, and a higher diastolic blood pressure were each associated with a lower mortality risk in Broste's thesis, some of which also contradict current knowledge.[5] As outcomes and statistical analysis methods in the original experiment were not clearly pre-specified, any subsequent statistical subanalyses of data should have been adjusted for multiple analysis inflation. This was not performed or acknowledged by Ramsden and colleagues, so the resulting observed associations could have arisen by chance.

Attrition bias

We used data in Broste's original thesis to analyse the extent of attrition in each group.[5] More than 83% of participants were lost to follow-up from both study arms (4028 out of 4814 from the

control arm, 3953 out of 4756 from the diet arm. All people lost to follow-up were excluded from further analysis and per protocol analysis was performed. Such analysis is likely to inflate estimated effect sizes.[7]

Secondly, 21 more deaths were observed in the diet group than the controls (269 versus 248), and this difference was exclusively driven by a higher mortality rate in those over 65 (19.9% (190) of 953 patients in the diet group and 16.9% (162) of 958 patients in the control group).[3 5] We manually counted events from Kaplan-Meier curves for participants over 65 who remained in the study for more than one year (when the mortality difference between diet and control groups became established). Twenty seven patients in the control arm and 40 patients in the diet group died during the 2nd year. Over the same period, however, 15 more participants were lost to follow-up from the control group (96) than the diet group (81) without explanation. Some of these 15 participants are likely to have died, as per protocol mortality rate during the 2nd year of study was 12% (27/225) in the control group. Considering the excessive attrition cases in the control group as deaths considerably alters the mortality rate estimates for those over 65 and halves the relative risk reduction to 0.075.

Unfortunately none of the reports of the experiment provide data to ascertain if prognostic equivalence between both groups in over 65s has been maintained through follow-up, which impairs the validity of any demonstrated effects.[8] Applying equivalent compensation for the higher rate of attrition in the control group to the overall population results in a higher mortality rate in the control group.

Wider relevance of findings

In addition to highly selective study population (mental hospital inpatients), the dietary interventions used in the experiment are a major barrier to external validity of the data. The World Health Organization currently recommends that no more than 30% of daily calories should come from fat.[9] The intervention and control diets in the experiments contained 38% and 39% of calories from fat, respectively. The American Medical Association recommends a daily intake of linoleic acid of between 5% and 10% of total energy content, with a note of caution for higher intakes (>11%) owing to an observed association with increased lipid peroxidation.[10 11] The proportion of energy from linoleic acid in the Minnesota Coronary Experiment was 13%, which was achieved by adding large quantities of liquid corn oil—practically the sole source of linoleic acid in the experiment. Such a diet might be harmful for reasons unrelated to the potential cholesterol mechanism and does not reflect current dietary recommendations. Even if the data are correct and

correctly interpreted, calls for a change to dietary guidelines are remiss as the recommendations do not reflect the diets offered to the control group in the experiment.

Summary

We need to advance our understanding of the interaction between dietary fat and human health. But the Minnesota Coronary Experiment has multiple methodological shortcomings, such as discrepant reporting, heavy attrition, and lack of wider relevance. Our detailed re-analysis empirically shows that any claims to change our current understanding of the relationship between saturated fat intake and mortality are not fully supported by data from the experiment.

<jrn>1 de Souza RJ, Mente A, Maroleanu A, et al. Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* 2015;351:h3978. PubMed doi:10.1136/bmj.h3978</jrn>
<jrn>2 Ramsden CE, Zamora D, Leelarthaepin B, et al. Use of dietary linoleic acid for secondary prevention of coronary heart disease and death: evaluation of recovered data from the Sydney Diet Heart Study and updated meta-analysis. *BMJ* 2013;346:e8707. PubMed doi:10.1136/bmj.e8707</jrn>
<jrn>3 Ramsden CE, Zamora D, Majchrzak-Hong S, et al. Re-evaluation of the traditional diet-heart hypothesis: analysis of recovered data from Minnesota Coronary Experiment (1968-73). *BMJ* 2016;353:i1246. PubMed doi:10.1136/bmj.i1246</jrn>
<bok>4 Frantz ID Jr, Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk. The Minnesota Coronary Survey. *Arteriosclerosis* 1989;9:129-35. PubMed doi:10.1161/01.ATV.9.1.129</jrn>
<jrn>5 Broste SK. *Lifetable analysis of the Minnesota Coronary Survey*. The University of Minnesota, 1981.</bok>
<jrn>6 Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. PubMed doi:10.1136/bmj.d5928</jrn>
<jrn>7 Abraha I, Cherubini A, Cozzolino F, et al. Deviation from intention to treat analysis in randomised trials and treatment effect estimates: meta-epidemiological study. *BMJ* 2015;350:h2445. PubMed doi:10.1136/bmj.h2445</jrn>
<jrn>8 Dumville JC, Torgerson DJ, Hewitt CE. Reporting attrition in randomised controlled trials. *BMJ* 2006;332:969-71. PubMed doi:10.1136/bmj.332.7547.969</jrn>
9. World Health Organization. Healthy diet Factsheet. 2015. http://www.who.int/mediacentre/factsheets/fs394/en/
<jrn>10 Harris WS, Mozaffarian D, Rimm E, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. *Circulation* 2009;119:902-7. PubMed doi:10.1161/CIRCULATIONAHA.108.191627</jrn>
11. Fats and fatty acids in human nutrition: report of an expert consultation. *FAO Food Nutr Pap* 2010;91:1-166.