Letters

Prognosis in obesity

Older people should not be misinformed about being overweight

Editor—With reference to the editorial by Lean on prognosis in obesity,[1] advising apparently overweight older people to lose weight may do more harm than good. Evidence suggests that the risks of being "overweight" decrease with increasing age. On the basis of mortality, the ideal body mass index (BMI) is higher in older than young adults, with an optimum BMI for people older than 65 in the young adult "overweight" range of 27-30 kg/m^2.[2] In a systematic review, Heiat et al concluded that the relation between BMI and mortality in people older than 65 is a flat bottomed, U-shaped curve, with mortality rising only at BMI >31 kg/m^2 and perhaps not at any BMI in people older than 75.[2]

Weight loss is more common than weight gain in older people, and associated with poor outcomes, even when the weight loss is intentional and the person was "overweight" at baseline.[3–5] In the prospective cardiovascular health study of some 4700 community dwelling people older than 65, weight loss of more than 5% over three years was substantially more common than weight gain of more than 5%.[3] Weight loss, but not weight gain, was associated with a significantly increased risk of mortality (relative risk 1.67, 95% confidence interval 1.29 to 2.15).[3] The association of increased mortality with weight loss persisted even at the highest third of baseline weight.[3] In a study of older men with BMI ≥30 kg/m^2, intentional weight loss was associated ($P<0.001$) with a greater rate of hip bone loss (−1.7%/year) than in men with no weight loss (−0.1%/year) or weight gain (0.5%/year).[5]

The indiscriminate application of evidence from studies in younger adults to the management of older people is hazardous. We believe that many older people are trying to lose weight inappropriately. There is a need to ensure that most of our elders are given appropriate advice: "Keep physically active, eat sensibly, and maintain weight."

Renuka Visvanathan *senior lecturer in geriatric medicine*
renuka.visvanathan@adelaide.edu.au
Ian Chapman *associate professor*
Department of Medicine, University of Adelaide, SA 5011, Australia

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Obstacles must be removed to prevent obesity through increased physical activity

Editor—In his editorial Lean proposes that we all eat a little less (0.418 mJ/day) and walk a little more (0.418 mJ/day, equivalent to 2000 steps) to prevent 90% of obesity.[1] If such recommendations work, they may seem a reasonable sacrifice for individual people and therefore could work in practice. To promote physical activity, however, we as a society face ever larger obstacles, mainly increased stress and an increasingly hostile environment (car clogged streets, threat of crime, and lack of parks and bicycle lanes). Moreover, we now have more calorie saving machines than ever—cars, lifts, computers, electric toothbrushes, etc—with more labour saving gadgets being developed and marketed on a seemingly daily basis.

Today the average adult in western Europe walks about 8000-9000 steps daily. Among the Amish people in North America, who refrain from using electricity and cars, men accumulate 18 425 steps daily (0% obesity) and women 14 196 (9% obesity).[2] The promotion of lifestyle physical activity, carried out as a routine part of daily living as practised by the Amish, is critical for long term adherence. A similar but more realistic strategy for promoting longstanding physical activity routines is physically active transport, such as walking to and from the bus stop or bicycling to and from work. The current trend, however, is that we drive shorter and shorter distances, with public transport services deemed too unreliable and slow.

We need to provide people with a realistic chance of achieving the necessary lifestyle change—for example, by creating car free areas where people live; safe and well lit parks and bicycle lanes, especially between the home and school or work; reliable public transport; shower facilities at work; and reduced perceived time pressures. We also need careful analysis of lifestyle change recommendations—is their efficacy established, can they be converted into practice?

Erik Hemmingsson *health educator*
Obesity Unit, Karolinska University Hospital, SE-141 86 Stockholm, Sweden
erik.hemmingsson@medhs.ki.se

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1 Lean MEJ. Prognosis in obesity. *BMJ* 2005;330:1339-40. (11 June.)
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Obesity in severe mental illness poses particular problems

Editor—Lean's editorial on prognosis in obesity is a timely contribution to the literature on the relation between increasing weight and physical morbidity and mortality in the general population.[1] Obesity is also a problem in people with severe mental illness. Major depressive disorder, bipolar disorders, and schizophrenia rank among the top 10 causes of disability worldwide,[2] and this group of patients has excess physical morbidity and reduced life expectancy (less than half of which is accounted for by suicide[3]).

Metabolic diseases, including obesity, are likely to contribute to increased mortality in this population. Whether mental illness in itself is an independent risk factor for the development of obesity and other components of the metabolic syndrome or whether metabolic dysfunction is simply secondary to lifestyle remains unclear. Iatrogenic causes of obesity are also likely to be important as atypical antipsychotic drugs—a commonly prescribed class of psychotropic drugs—cause weight gain, disorders of glucose homeostasis, and hyperlipidaemia.[4] A high prevalence of undiagnosed and untreated metabolic disease, including obesity, has recently been reported in psychiatric patients taking antipsychotic drugs,[5] which may reflect poor monitoring and intervention owing to a lack of awareness in primary and secondary care of this important public health issue. Recent consensus statements

make clear the need for monitoring metabolic disease in patients prescribed antipsychotic drugs.[4]

Although the first law of thermodynamics ("move a little more, eat a little less"[1]) may hold scientific truth and credibility for people motivated to lose weight and potentially increase longevity, many of the core psychopathological features of patients with severe mental illness (depressed mood, lack of motivation, hopelessness, disorganised thinking, etc) conspire against such lifestyle changes.

Paul Mackin *academic specialist registrar in psychiatry*
paul.mackin@ncl.ac.uk
Allan H Young *professor of psychiatry*
Department of Psychiatry, University of Newcastle upon Tyne, Royal Victoria Infirmary, Newcastle upon Tyne NE1 4LP

Competing interests: None declared.

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Author's reply

Editor—In principle it is correct to consider whether advice to younger people is appropriate to older people. With regard to obesity, the evidence on intentional weight loss is scanty and mainly based on self reports. Our study of intentional (at least intended) and measured weight loss among older patients with type 2 diabetes (mean age 64) followed up as a cohort until death, showed a strong positive association with life expectancy: weight loss of 10 kg was associated with three to four years' increased survival.[1]

However, it should be remembered that obesity is not primarily a killing disease. Its main impact, increasingly with age, is on disability and quality of life through aggravation of a vast range of symptoms, including tiredness, breathlessness, back pain, arthritis, stress incontinence, depression—and the list goes on.

Hemmingsson has called for proper evaluation of diet and physical activity interventions to prevent obesity. A reluctance remains to fund proper evaluation of preventive interventions. The development and evaluation of a new drug to reduce a cardiovascular risk factor, and possibly delay cardiac events by a few weeks, now costs well over £200-500m. The development and evaluation of an evidence based intervention to manage obesity by diet and exercise in primary care, the Counterweight programme,[2] cost about £5m. A recent proposal to develop and evaluate a family based programme to prevent weight gain, obesity, and metabolic consequences, based on America on the Move and using the existing Counterweight team, was costed at £835 000 and was not even evaluated as a full proposal when submitted to the Medical Research Council under the National Prevention Research Initiative, whose total budget for all disease prevention was only £12m.

Mackin and Young refer to the invidious cycle between weight gain and mental ill health, which conspires against making sustainable lifestyle changes for losing weight. This issue is particularly serious for patients prescribed the many antipsychotic drugs that stimulate increased food consumption. Mackin and Young are right: the priority should be primary prevention of excess and unwanted weight gain in adults.

M E J Lean *professor*
lean@clinmed.gla.ac.uk
Division of Developmental Medicine, Human Nutrition, University of Glasgow, Royal Infirmary, Glasgow G31 2ER

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1 Lean MEJ, Powrie JK, Anderson AS, Garthwaite PH. Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 1990;3:228-33.
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Early life risk factors for obesity in childhood

The hand that rocks the cradle rules the world

Editor—The survey by Reilly et al to identify the risk factors for obesity in children seems to have been well designed, meticulously conducted, and rigorously analysed. [1] But as someone who is neither especially numerate nor an expert in this research topic, I had to read the paper three times and consult a statistician colleague to confirm that the authors had systematically controlled for maternal education—a proxy for social class—in every item in their analysis.

In other words, in their conclusion "Eight factors in early life are associated with an increased risk of obesity in childhood," the authors might (for the benefit of the general practitioner on the Clapham omnibus) have inserted the qualifier "that is, AFTER controlling for maternal education, which was confirmed by this study to be highly significantly related to the development of obesity in children."

Having (rightly, I'm sure, from a statistical standpoint) controlled so carefully for maternal education, the authors then do not mention it in their discussion of potentially modifiable risk factors for childhood obesity. Their recommendations seem to focus on technical tweaks targeted at metabolic variables, but my own hypothesis as a general practitioner is that interventions aimed at increasing the health literacy of the primary caregiver have far greater potential for achieving a slimmer cohort of primary school children.

I would value comment on this suggestion from both the authors and practitioners who try to influence the rate of weight gain of their youngest patients.

Trisha Greenhalgh *professor of primary health care*
University College London, London N19 5LW
p.greenhalgh@pcps.ucl.ac.uk

Thanks to Richard Morris for advice on the statistical aspects of the paper.
Competing interests: None declared.

1 Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. Early life risk factors for obesity in childhood: cohort study. *BMJ* 2005;330:1357. (11 June.)

Early feeding is crucial target for preventing obesity in children

Editor—Reilly et al present their findings on some early life risk factors for obesity at age 7 in a cohort of 7758 children born in the early 1990s.[1] We believe that their conclusions about breast feeding and time of weaning are flawed.

The investigators infer that these early feeding factors are unimportant because they are not independently associated with the obesity outcome in a statistical model that includes more proximal, parental, and prenatal factors. If early feeding factors exert their influence on childhood obesity largely through a causal pathway that includes other factors in the investigators' statistical models then it is not surprising that the early feeding factors do not emerge as independent predictors: it is a mistake to infer that these factors are therefore unimportant. The central public health issue is to identify the modifiable risk factors that can reasonably be assumed to be causal for obesity in children.

We believe that there is sufficient bio-behavioural and epidemiological evidence to support the idea that infant feeding practice directly affects early weight gain, and that trials of early feeding interventions to prevent later obesity in children are justified.[2–5] The investigators' univariate findings that early feeding factors predict later obesity add to this evidence, and their multivariate results should not be used to weaken the evidence on grounds of specious confounding. These data could be reanalysed with more attention paid to plausibly causal pathways.

Iain E Buchan *senior lecturer*
buchan@manchester.ac.uk
Richard F Heller *professor*
Peter Clayton *professor*
Medical School, University of Manchester, Manchester M13 9PT

Peter E Bundred *reader*
Department of Primary Care, University of Liverpool, Liverpool L69 3GB

Tim J Cole *professor*
Institute of Child Health, University College London, London WC1N 1EH

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Authors' reply

Editor—Greenhalgh and Buchan et al focus on interpretation of our results and the implications for obesity prevention. We adjusted for maternal education because it influenced both the potential risk factors and the outcome (obesity). Greenhalgh highlights the importance of socioeconomic status, although all social groups have been affected by the obesity epidemic.[1] Targeting maternal education may be useful in obesity prevention, but there is currently no (maternal) educational or socioeconomic intervention that successfully prevents obesity in children.[2]

Buchan et al recommend early feeding factors as targets of obesity prevention initiatives. Our results do not rule out a role for infant feeding as a cause of obesity. Breast feeding was protective against later obesity in two out of three statistical models, but not in our final model for reasons discussed in the paper. Evidence for timing of introduction of complementary foods, derived from analysis of 21 potential risk factors in the entire sample, was inconclusive. A systematic review was not supportive of timing of introduction of complementary feeding as a risk factor,[3] and it is unlikely that it could have operated via the other factors in our final model (birth weight, parental obesity, sleep, and TV viewing at age 3) as suggested by Buchan et al. However, a more detailed analysis of a wider range of early feeding factors would be desirable.

Preventive interventions for childhood obesity should meet certain criteria.[4 5] At present, these criteria may be met by few strategies: promoting breast feeding, reducing sedentary behaviour, and reducing the consumption of sugar sweetened drinks. Future interventions are probably most likely to succeed if they target these behaviours. Attempting to modify timing of introduction of complementary feeding might be beneficial in other respects but seems premature as a strategy for obesity prevention at this stage.

John J Reilly *reader in paediatric energy metabolism*
jjr2y@clinmed.gla.ac.uk
Julie Armstrong *lecturer in nutrition*
University of Glasgow Division of Developmental Medicine, Yorkhill Hospitals, Glasgow G3 8SJ

Pauline Emmett *senior research fellow in nutrition*
Andy Ness *senior lecturer in epidemiology*
Andrea Sherriff *research fellow in medical statistics*
Unit of Paediatric and Perinatal Epidemiology, Institute of Child Health, University of Bristol

Competing interests: None declared.

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Obesity in middle age and future risk of dementia

Problem is probably greater for women

Editor—The paper by Whitmer et al supports the findings of an earlier study in showing that obesity in middle age predicts dementia in older age.[1 2] The major apparent weakness of the study is the loss of 13 014 patients to follow-up. Their adiposity and sociodemographic characteristics at study entry (1964-73: n = 25 290) were reported to be the same as those who were followed up to 1994-2003. That is important. Their medical and physical characteristics are also important. We are left to accept that they were similar also. The similarity or otherwise needs to be presented with the paper.

Table 1 shows some marked differences among the people who were later diagnosed with dementia: education to grade school level only (11.1%) compared with additional education (6.9%), black race (8.9%) compared with white race (7.1%) and Asian or other races (5.5%). Adjustment for these confounders did apparently not modify the risk of the diagnosis of dementia related to obesity significantly.

The effect of obesity and overweight was more apparent in women. The lesser effect of obesity in men is dealt with by the statement that there were fewer obese and overweight men and that the power to detect an effect was therefore reduced. It is, however, clear from the text and table 2 that there were in fact more obese and overweight men (n = 2546) than women (n = 1804).

Further confusion arises from consideration of the sister paper derived from the same database.[3] In that paper the effects of midlife risk factors (smoking, hypertension, cholesterol, and diabetes) on the subsequent diagnosis of dementia are reported. The exclusion of people with missing data reduces to 8845 the numbers followed up to 1994-2003. Fewer subjects have not been diagnosed with dementia (8124 *v* 9563), yet more are so diagnosed (721 *v* 713). How that came about is difficult to explain unless the follow-up was longer. Reading the two papers together indicates no difference in time bases for acquisition of the data.

Despite problems the paper by Whitmer et al shows that dementia in women (probably) and in men (possibly) is influenced by obesity in the middle of life and late life and overweight, determined by body mass index, and supported by measures of skinfold thickness. A study from Sweden generated similar conclusions, applicable to women but not to men.[4]

Alan J Goble *cardiology consultant*
Heart Research Centre, Melbourne, VIC 3050, Australia
heart@medicine.unimelb.edu.au

Competing interests: None declared.

1 Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 2005;330:1360-2. (11 June.)
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Dietary fat and sugar may hold the clue

Editor—Whitmer et al report further evidence supporting the association between obesity and dementia.[1] Although the mechanism is still far from being understood, the authors alluded to the involvement of adiposity with inflammation and its markers.

One possible mechanism linking obesity with dementia is oxidative stress resulting from an increased intake of processed sugars and fats, which is the hallmark of the modern diet. Rats maintained on a diet high in refined sugar and fat generated higher concentrations of free radicals.[2 3] In contrast, caloric restriction in animals leads to reduced production of free radicals by mitochondria and increased longevity.[4]

Whitmer et al acknowledge that the lack of nutritional assessment was a limitation of their study. If such data had been available they would have shed light specifically on a possible relation between fat and sugar intake and risk of dementia, especially as a diet rich in these substances is linked to obesity. We recently showed that patients with dementia eating a diet high in fat and carbohydrates have an increased blood activity of glutathione peroxidase, an endogenous antioxidant, which may be a compensatory response to an increased oxidative stress in dementia.[5]

Whitmer et al say that all cause dementia diagnoses included dementia, Alzheimer's disease, and vascular dementia.[1] However, their data did not include differentiation between these subsets, especially between Alzheimer's disease and vascular dementia. Whether obesity was preferentially associated with either vascular dementia or Alzheimer's disease, or both, would be interesting, especially as the neuropathological aetiology of these two disorders is different.

Naji Tabet *senior lecturer in old age psychiatry*
Postgraduate Medical School, Faculty of Health, University of Brighton, Brighton BN1 9PH
n.t.tabet@brighton.ac.uk

Competing interests: None declared.

1 Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 2005;330:1360-2. (11 June.)

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Midlife obesity increases risk of future dementia

Editor—Whitmer et al reported a prospective study showing that obesity in middle age was associated with increased risk of future dementia.[1] However, little information was given on the types of dementia. This is important especially in Alzheimer's disease, in which vascular risk factors might contribute to its development.[2] We have investigated the relation between Alzheimer's disease and obesity throughout adult life in a small case-control study.

We recruited 25 patients with probable Alzheimer's disease from the Launceston Memory Disorders Clinic, Tasmania, and 50 controls from the local community. Patients were living at home and were physically well, with no important medical problems. Current height, weight, and waist circumference were measured. In addition, we asked participants to recall their weight at the age of 20-25 and 40-45. Self reported weight has been shown to be highly correlated with direct measurement in cognitively healthy people and those with mild to moderate dementia.[3 4]

The mean age of patients with Alzheimer's disease and controls was 74.9 (range 57-88) and 72.1 (65-94), respectively. The mean mini-mental state examination score was 19.0 (4-26) for patients with Alzheimer's disease and 29.6 (28-30) for controls. Most patients had mild to moderate disease (80% with scores greater than 14). The table shows that at midlife, patients with Alzheimer's disease had higher body mass index (BMI) by 2.8 kg/m^2 or 12% than controls. At late life, BMI was not significantly different, but the waist circumference in patients with Alzheimer's disease was higher than in controls by 6.1 cm, or 7%.

Our study supports the conclusion of Whitmer et al that midlife obesity increases the risk of future dementia, in this case Alzheimer's disease. In addition, abdominal obesity, which is highly associated with insulin resistance and cardiovascular diseases, might also be a risk factor for Alzheimer's disease.

George Raza *senior lecturer in geriatric medicine and director of research*
george.razay@dhhs.tas.gov.au
Anthea Vreugdenhil *research coordinator*
Launceston General Hospital, Launceston, Tasmania 7250, Australia

Competing interests: None declared.

1 Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, Yaffe K. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* 2005;330:1360-2. (11 June.)
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Authors' reply

Editor—The study that Goble referenced as also investigating midlife obesity and dementia was conducted in subjects with obesity measurements at age 70.[1]

Goble questions whether the midlife health status of those who left the health plan was similar to those who remained, and the comparison of dementia cases between this study and another from the same cohort.[2] The midlife physical characteristics (cholesterol, blood pressure, and diabetes) did not differ between those who left or stayed in the plan. The eight count difference in dementia cases in our two studies is the result of a difference in cohorts based on age categorisation in midlife and availability of adiposity data.

Dementia had a lower prevalence in men than in women (6.7 % *v* 7.11 %). The power to detect effects may therefore be slightly reduced in men. Additionally, men were slightly less likely to be obese (9.97% *v* 10.1%). A much greater proportion of men than women was overweight (48% *v* 25%), and the magnitude as well as the significance of the hazard ratio for overweight men was much smaller than that for women.

This could have several reasons, including competing risk, or a true sex difference in the effect of body mass index (BMI) on risk of dementia. The most likely explanation seems to be that the standard cut-off points set by the World Health Organization for overweight may be an insensitive measure of adiposity. BMI tends to overestimate adiposity in those with high muscle and bone mass; therefore some men in the overweight category may have had an "overweight" BMI but low actual adiposity.[3] This is substantiated by the fact that we found no significant sex differences in the effect of skinfold thickness on risk of dementia—the effect of subscapular skinfold thickness was even stronger in men (hazard ratio 1.97 (95% confidence interval 1.36 to 2.85)) than women (1.52 (1.11 to 2.08)). If adiposity and risk of dementia in men were not associated, then we would not have seen an effect of skinfold thickness on risk of dementia in men as well as women.

We disagree with Goble that the problem is for women only, an earlier larger study from Sweden of men only found that overweight and obese categories of BMI increased risk of dementia.[4] Goble cites this study as that of women only.

We could not present risks of BMI and skinfold thickness associated with subtypes of dementia since most of our diagnoses came from primary care doctors, and were coded as "dementia." Our future work will focus on risk factors for dementia subtypes in our population.

Razay and Vreugdenhil's confirmatory findings in a case-control study that late life waist circumference is greater in patients with Alzheimer's disease are especially interesting because of the implications of the effects of central adiposity and the metabolic syndrome on cognitive health.[5]

Rachel Whitmer *gerontological epidemiologist*
raw@dor.kaiser.org
Charles P Quesenberry Jr *senior biostatistician*
Division of Research, Kaiser Permanente, Oakland, CA 94612, USA

Kristine Yaffe *associate professor*
Department of Psychiatry, University of California, San Francisco, CA, USA

Competing interests: None declared.

1 Gustafson D, Rothenberg E, Blennow K, Steen B, Skoog I. An 18-year follow-up of overweight and risk of Alzheimer disease. *Arch Intern Med* 2003;163:1524-8.
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Means (standard errors) and logistic regression odds ratios (per standard deviation) for BMI and waist circumference, adjusted for age, sex, years of education, cigarette smoking, and alcohol consumption

Variable (SD)	Patients with Alzheimer's disease	Controls	Odds ratio (95% CI)
BMI at age 25 (3.5 kg/m^2)	23.5 (0.9)	22.8 (0.5)	1.16 (0.64 to 2.10)
BMI at age 45 (3.9 kg/m^2)	27.1 (0.9)	24.3 (0.6)*	2.06 (1.01 to 4.21)
BMI at age 65+ (4.1 kg/m^2)	26.5 (1.0)	25.5 (0.6)	1.24 (0.68 to 2.26)
Waist circumference (11 cm)	88.4 (3.3)	82.3 (3.2)*	2.05 (0.99 to 4.26)

P<0.05, calculated by using general linear model analysis.
BMI=body mass index

Include measurement of waist circumference in GP contract

Editor—Abdominal obesity, as measured by waist circumference, is a key predictive measurement of metabolic and cardiovascular risk, more accurate than the measurement of body mass index (BMI) alone.[1]

Although there is some debate over the exact threshold, the principle is clear—a measurement of over 100 cm is regarded as substantially increasing risk in men. Waist circumference should be used as a standard test to ensure the accurate assessment of patients at high risk of metabolic and cardiovascular disease and be given the

same importance as routine blood pressure or cholesterol checks.

Abdominal obesity is a measure of excess visceral fat. Visceral fat, the accumulation of adipose tissue within the omentum, abdomen, and around abdominal organs can be assessed simply by measuring waist circumference. It is a key factor in the development and progression of cardiovascular disease. The close proximity of visceral fat to the hepatic portal circulation, and the cytokines (including tumour necrosis factor α, interleukin-6, and C reactive proteins) secreted by the adipocytes may directly influence risk factors associated with the development of cardiovascular disease.[2] Waist circumference is therefore an effective and simple tool that could be integrated into general practice.

Weight reduction in obese patients at risk of cardiovascular disease is associated with an improvement in metabolic factors and improved glycaemic control.[3] A modest reduction in weight of 5-10% has been shown to lead to notable reductions in blood pressure, thrombogenic potential, and inflammatory markers, as well as improvements in lipid profile and insulin sensitivity.[4] Recent studies support the benefits of reducing waist circumference to improve metabolic parameters and cardiovascular risk.[5]

An urgent need therefore exists to include the measurement of waist circumference in the current review of the GP contract (GMSII). Its inclusion would enable both easier identification of high risk patients and earlier implementation of management strategies.

David Haslam *chair, National Obesity Forum*
Nottingham NG2 5PA
johnny@fuelrefuel.com

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Six additional authors are on bmj.com

Audit is important part of drug safety and regulation

Editor—Waller et al write about the responsibilities of the pharmaceutical companies and the regulating agencies such as the UK Medicines and Healthcare products Regulatory Agency to improve the safety of the drugs that are licensed for prescription.[1] Although cyclo-oxygenase 2 inhibitors and selective serotonin reuptake inhibitors have been under the spotlight in recent months, other drugs may be of greater concern.

In 2000 the National Institute for Health and Clinical Excellence (NICE) issued guidance on the use of proton pump inhibitors in treating dyspepsia.[2] In January 2005 in our hospital, an audit of record of 50 deceased patients identified 20 who were taking these drugs. Twelve of the 50 patients had had *Clostridium difficile* isolated in recent months, and eight of them had been taking proton pump inhibitors. Forty three patients received one or more antibiotics, 29 received three or more (cephalosporins 27, co-amoxiclav 19, metronidazole 19, clarithromycin 14; five or fewer had received nine other antibiotics).

Studies in Plymouth in 2003 and Montreal in 2004 indicated that using proton pump inhibitors, especially in the long term, compounded with other precipitators such as multiple antibiotic usage and nasogastric feeding, more than doubled the incidence of infection with *C difficile*.[3 4]

As a profession, we have the responsibility to follow the advice of agencies such as NICE about prescribing and to audit the effects of our treatments on our patients. We are looking at deceased patients' records in blocks of 50 using some of the trigger tools recommended by the Institute for Healthcare Improvement.

This audit has led to several improvements already and highlighted the rapidly increasing popularity of proton pump inhibitors for infirm elderly people, who are most at risk of *C difficile* infection. Although some of these patients with *C difficile* died as a result of the organism's effects, the new North American strain was not identified.

Michael I Carter *consultant anaesthetist*
Michael.Carter@ldh-tr.anglox.nhs.uk
Jane Murkin *patient safety manager*
Luton and Dunstable Hospital NHS Trust, Luton LU4 0DZ

Competing interests: None declared.

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Dissemination of results needs to be tracked as well as the funding is

Editor—Decullier et al evaluated some of the factors influencing publication of health related research projects.[1] They examined research activity outcomes from the perspective of research ethics approval.

Registration of clinical trials is not universally required, and sponsor databases are necessarily limited in scope. However, approval by a research ethics committee is required for all research on human subjects and includes protocols regardless of funding status and origin. We agree with this approach and believe that research ethics approval is the earliest convergence in the birth of research projects on human subjects and an ideal perspective from which to study the subsequent events in a project's life cycle.

Failure to disseminate results is considered to be research misconduct and is an urgent scientific and ethical concern.[2 3] As confirmed by Decullier et al, selective dissemination of research results in publication bias, typically skewing the literature towards reports with positive findings. In their discussion, however, Decullier et al seem to conflate the issue of clinical trial registration with that of selective dissemination, implying that registration will remedy this situation.

Although the registration models promoted by the International Council of Medical Journal Editors, the Canadian Institutes of Health Research, European regulatory agencies, and others increase transparency, they are not designed to ensure that registered protocols result in publication but to ensure that publications are spawned only from registered protocols.

Preliminary results from a study we are undertaking in Canada indicate that, although meticulous financial records of research activity are kept, mechanisms for identifying and tracking the dissemination status of research projects including human subjects are almost non-existent.

We hope to build on the work of Decullier et al by characterising the range of dissemination (from local presentation to global distribution) that is relevant to clinicians in contemporary practice, identifying trends over time in modes of dissemination (oral, written, and electronic), and clarifying the mechanisms required to increase rates of dissemination as a means of enhancing the value, integrity, and the public's trust in clinical research.

James McCormack *professor*
jmccorma@interchange.ubc.ca
Peter Loewen *associate professor, part time*
Peter Jewesson *professor*
Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

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