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REVIEW

Putative contributors to the secular increase in obesity: exploring the roads less traveled

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Objective: To investigate plausible contributors to the obesity epidemic beyond the two most commonly suggested factors, reduced physical activity and food marketing practices.
Design: A narrative review of data and published materials that provide evidence of the role of additional putative factors in contributing to the increasing prevalence of obesity.
Data: Information was drawn from ecological and epidemiological studies of humans, animal studies and studies addressing physiological mechanisms, when available.
Results: For at least 10 putative additional explanations for the increased prevalence of obesity over the recent decades, we found supportive (although not conclusive) evidence that in many cases is as compelling as the evidence for more commonly discussed putative explanations.
Conclusion: Undue attention has been devoted to reduced physical activity and food marketing practices as postulated causes for increases in the prevalence of obesity, leading to neglect of other plausible mechanisms and well-intentioned, but potentially ill-founded proposals for reducing obesity rates.
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Introduction

The prevalence of obesity has increased substantially since 1970.[1] Although the causes are uncertain, many contend that environmental changes are almost certainly responsible and focus overwhelmingly on food marketing practices and technology and on institution-driven reductions in physical activity (the 'Big Two'), eschewing the importance of other influences. This has created a hegemony whereby the importance of the Big Two is accepted as established and other putative factors are not seriously explored. The result may be well-intentioned but ill-founded proposals for reducing obesity rates.

We begin by reviewing key facts about the secular increase in obesity ('the epidemic'). We then highlight evidence

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showing that the obesogenic influence of the Big Two is largely 'circumstantial', relying heavily on ecological correlations rather than individual-level epidemiologic data or randomized experiments. Subsequently, we delineate the evidence for 10 other putative factors for which the evidence is also circumstantial but in many cases, at least equally compelling. We conclude that undue attention has been devoted to reduced physical activity and food marketing practices as postulated causes for the epidemic, yielding neglect of other plausible mechanisms.

The epidemic

Obesity prevalence in the United States has been increasing for at least 100 years[2,] with an apparent acceleration in the past 3 decades. The distribution of body mass index (BMI; kg/m^2) has increased modestly in median and moderately in mean. What has increased far more dramatically is the positive (right-tailed) skewness of the distribution, such that the most obese segments of the distribution are far more obese than in years past. Obesity has increased in every age, sex, race and smoking-status stratum of the population, which has correctly been taken to indicate that changes in the distribution of age, race, sex and smoking status cannot completely account for the epidemic. However, as we show later, this finding does not indicate that changes in the distribution of these variables are not contributing to the epidemic.

Evidence for the Big Two

Reduced physical activity,[3] particularly from reduced school-based physical education,[4] and specific food manufacturing and marketing practices (e.g., vending machines in schools,[5] increased portion size,[6] increased availability of fast-food,[3,7,8] use of high-fructose corn syrup (HFCS)[9]) comprise the Big Two explanations proffered for the obesity epidemic and are frequently cited as targets of potential public health interventions. We do not intend to imply that the Big Two are not salient contributors to the epidemic. Rather, we offer that the evidence of their role as primary players in producing the epidemic (as well as the evidence supporting their potential ability to reverse the trend if manipulated) is both equivocal and largely circumstantial – that is, the hypothesized effects are underdetermined by the data. Data rarely, if ever, stem from randomized controlled trials of the effects in population settings and in many cases do not even include a consistently supportive body of individual-level epidemiologic studies. The arguments for the effects of each subcomponent tend to rely heavily (although not exclusively) on presumed mechanisms of action and ecological studies[10] in which associations between the putative factor and obesity rates are shown at the aggregate population level across times or geographic locations. According to the Food and Drug Administration,[11] because ecological 'studies do not examine the relationship between exposure and disease among individuals, the studies have been traditionally regarded as useful for generating, rather than definitively testing, a scientific hypothesis.' Consider several examples. Regarding physical education classes, *Pathways*, a large, expensive and expertly designed childhood obesity prevention program emphasized increasing frequency and quality of physical education classes and found no effect on BMI.[12] Regarding vending machines, a thorough evidence-based review (MS Faith *et al*., unpublished, 2005) found no published randomized trials, quasi-experiments or observational epidemiologic studies evaluating their effects on obesity. Regarding fast-food availability, although some studies showed associations with obesity, Burdette and Whitaker[13] found no association between being overweight and proximity to fast-food restaurants in over 7000 children. Regarding HFCS, the leading source (in the United States) is sweetened beverages and three out of four studies conducted in children have found no association between soft drink consumption and BMI when controlling for total energy intake,[14–17] raising the issue that there is no independent effect of HFCS calories on body weight, other than its pleasant taste possibly leading to the potential increase in total caloric intake as would any food.

Regarding TV viewing, a recent meta-analysis concluded 'A statistically significant relationship exists between TV viewing and body fatness among children and youth although it is likely to be too small to be of substantial clinical relevance. …media-based (TV-based) inactivity may be unfairly implicated in recent epidemiologic trends of overweight and obesity among children and youth.'[18] Regarding portion size, Rolls has presented considerable evidence that portion size may increase daily food intake. Nevertheless, Rolls[19] wrote, '… that adults who are obese eat bigger portions of energy-dense foods do[es] not prove that portion size plays a role in the etiology of obesity. Indeed, at this time we know of no data showing such a causal relationship.'

Again, these data and quotations do not disprove the importance of those factors listed but highlight their less-than-unequivocal evidential basis. Realizing this should serve as an impetus for more vigorous consideration of additional factors.

Additional explanations for the increase in obesity

We do not review all plausible contributors to the epidemic but select those that are most interesting and for which the totality of current evidence is strongest. Figure 1 portrays the secular increase in a number of key indicators of these putative causal influences. For most Additional Explanations, we offer the conclusion that a factor (e.g., *X*) that has contributed to the epidemic will logically follow acceptance of two propositions: (1) *X* has a causal influence on human adiposity and (2) during the past several decades, the frequency distribution of *X* has changed such that the relative frequency of values of *X* leading to higher adiposity levels has increased. In the absence of countervailing forces,

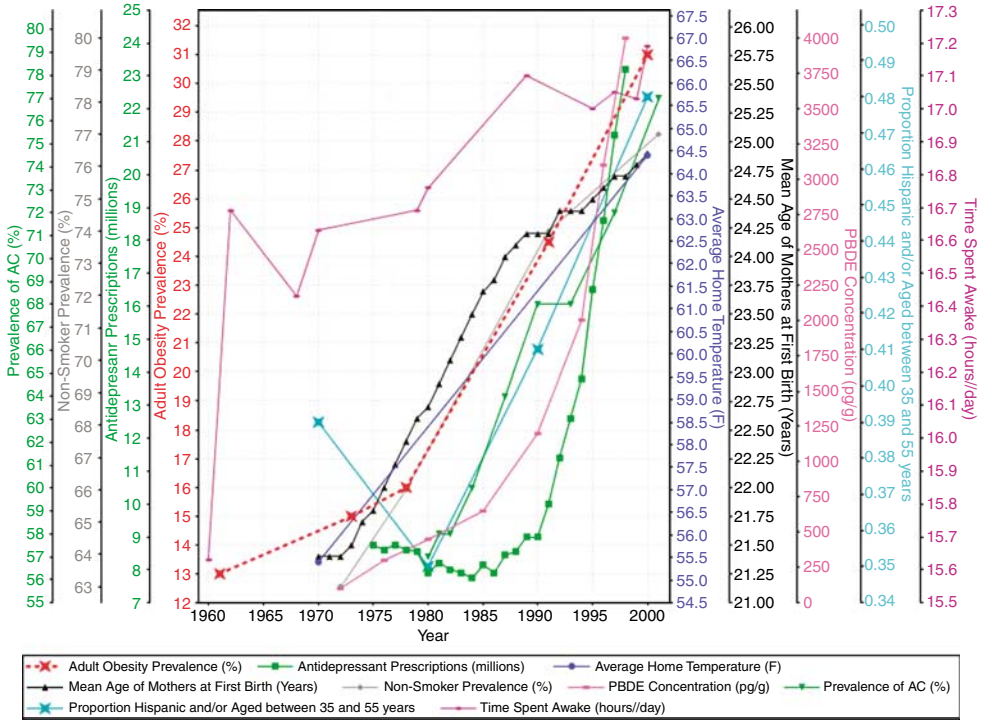

Figure 1 Secular changes in a number of key indicators of factors that may be related to the increase in obesity. These indicators include the following: mean age of US mothers at first birth;[77] antidepressant prescribing in the UK;[115] prevalence of AC – the percentage of US households equipped with air-conditioning;[49] UK average internal home temperature – average internal home temperature;[46] PDBE concentration—the concentration of polybrominated diphenyl ethers in the breast milk of Swedish women from 1972 to 1978;[39] proportion of US adult population that is Hispanic and/or between 35 and 55 years of age;[71] time spent awake;[27,28] non-smoker prevalence (Data compiled by the Centers for Disease Control and Prevention, Office on Smoking and Health, from the Current Population Survey, 1955, and the National Health Interview Surveys, 1965–1994, unpublished);[50,53] adult obesity prevalence, US adults only, BMI $\geqslant 30\,kg/m^2$ indicates obesity.[1]

if both propositions are true, obesity levels will increase. Therefore, for postulated factors supported by this line of propositional argument (Additional Explanations 1–7), we evaluate evidence addressing whether the factor can increase fatness and whether the factor's frequency distribution has changed in the obesogenic direction. For the remaining Additional Explanations, propositional arguments vary in form and are outlined separately.

Additional Explanation 1: sleep debt

Evidence that less sleep can cause increased body weight

For children and adults, hours of sleep per night is inversely related to BMI and obesity in cross-sectional studies and incident obesity in longitudinal studies.[20,21] In animals, sleep deprivation produces hyperphagia, offering a mechanism of action.[22] Evidence for the physiologic mechanism includes decreased leptin and thyroid-stimulating hormone secretion, increased ghrelin levels and decreased glucose tolerance, all endocrine changes that occur with sleep deprivation.[23–25] Sleep restriction in humans has recently been shown to produce similar effects, including increased hunger and appetite.[26] These changes are consistent with chronic sleep deprivation leading to increased risk of obesity.

Has average sleep debt increased?

Data clearly show that the average amount of sleep has steadily decreased among US adults and children during the past several decades.[27,28] Average daily sleep has decreased from over 9 to just over 7 h among adults.

We note that future studies examining the association between sleep debt on BMI or any cause–effect link between them would benefit from utilizing more objective assessments of sleep duration and sleep quality (vs self-reporting). A good example is the measure of spontaneous physical activity during sleep measured by microwave radar detector. Bitz *et al*.[29] used this technique in finding increased sleep disruptions among diabetic subjects. Resta *et al*.[30] found that even in the absence of sleep apnea, obese subjects were observed to suffer more sleep disruptions defined as higher sleep latency, a lower percentage of REM sleep and a lower sleep efficiency (a ratio between total sleep time and time spent in the bed) than non-obese subjects. The effect of age

should be controlled in such assessments, as it correlates positively with sleep time activity.[29] Large-scale self-report studies could also be improved with subjects' use of actigrophy watches to verify self-reported sleep times.

Additional Explanation 2: endocrine disruptors

Evidence that endocrine disruptors can increase adiposity
Endocrine disruptors (EDs) are lipophilic, environmentally stable, industrially produced substances that can affect endocrine function and include dichlorodiphenyltrichloroethane, some polychlorinated biphenols and some alkylphenols. By disturbing endogenous hormonal regulation, EDs may fatten through multiple pathways. Consider the effect of estrogen on white adipose tissue: in rodents, white adipose is increased by ovariectomy and decreased by estrogen replacement therapy.[31] Similarly, postmenopausal women have increased white adipose tissue, which is reduced by estrogen replacement therapy.[32] The estrogen receptor-α knockout mouse has increased white adipose tissue in mice of both sexes.[33] Some EDs directly bind to nuclear receptors, including the peroxisome proliferator-activated receptor γ and the retinoic acid X receptor. Kanayama *et al*.[34] found that the organontin EDs are high-affinity agonists for the peroxisome proliferator-activated receptor γ and retinoic acid X receptor and stimulate adipocyte proliferation. Other EDs are antagonists of certain nuclear receptors. For example, vinclozolin is a dicarboximide fungicide and an androgen receptor antagonist.[35] Some EDs are antiandrogens[36] and may thereby alter nutrient partitioning toward a more fatty body composition. Endocrine disruptors can also inhibit aromatases[37] and the aromatase knockout mouse has increased adiposity. In humans, body ED burden and BMI or fat mass are positively correlated, even when normalized to total body triglyceride.[38]

Evidence that endocrine disruptors exposure has increased
Endocrine disruptors have increased in the food chain.[39,40] One example indicator is that polybrominated diphenyl ether concentration in Swedish women's breast milk almost doubled every 5 years from 1972 to 1998.[39]

Additional Explanation 3: reduction in variability in ambient temperature

Evidence that remaining in the thermoneutral zone promotes adiposity
The thermoneutral zone (TNZ) is the range of ambient temperature in which energy expenditure is not required for homeothermy. Exposure to ambient temperatures above or below the TNZ increases energy expenditure, which all other things being equal, decreases energy stores (i.e., fat). This effect was shown in short-term controlled human experiments[41,42] and the decreases in adiposity were evident in controlled animal experiments; these effects are widely exploited in livestock husbandry, where selecting the environment to maximize weight gain is critical.[43]

Animal[44] and human[45] studies show that excursions above the TNZ markedly reduce food intake. Herman[45] cited a consumer survey suggesting that after an air-conditioning breakdown, restaurant sales drop dramatically.

Evidence that time in the thermoneutral zone has increased
Humans dwell more in the TNZ than they did 30 years ago. For example, the average internal UK home temperature increased from 13 to 18°C between 1970 and 2000.[46] The US thermal standard for winter comfort increased from 18°C in 1923 to 24.6°C in 1986.[47,48] The percentage of US homes with central air-conditioning increased from 23 to 47% between 1978 and 1997, whereas the percentage of homes with no air-conditioning decreased from 44 to 28%. In the Southern United States, where some of the highest obesity rates are observed, the percentage of homes with central air-conditioning increased from 37 to 70% between 1978 and 1997, and the percentage of homes without any air-conditioning decreased from 26 to 7%.[49]

Additional Explanation 4: decreased smoking

Evidence that smoking reduces weight
Epidemiologic and clinical studies consistently show that smokers tend to weigh less than non-smokers and weight gain follows smoking cessation.[50,51] Nicotine has both thermogenic and appetite-suppressant effects and its effects on appetite are enhanced by caffeine.[52]

Evidence that smoking rates have decreased
Rates of cigarette smoking among US adults steadily declined during the past several decades.[53] Centers for Disease Control and Prevention scientists estimated that between 1978 and 1990, smoking cessation was responsible for about one-quarter (2.3 of 9.6 percentage points) of the increase in the prevalence in overweight in men and for about one-sixth (1.3 of 8.0 percentage points) of the increase in women.[50]

Additional Explanation 5: pharmaceutical iatrogenesis

Evidence that certain pharmaceuticals increase weight
Weight gain is induced by many psychotropic medications (antipsychotics, antidepressants, mood stabilizers), anticonvulsants, antidiabetics, antihypertensives, steroid hormones and contraceptives, antihistamines and protease inhibitors. Selective serotonin reuptake inhibitors (antidepressants) may

also produce weight gain, but data are less consistent.[54–56] Almost all atypical antipsychotics produce markedly more weight gain than placebo or traditional antipsychotics. For olanzapine and clozapine, mean weight gains were over 4 kg at 10 weeks.[57] These drugs are active at many receptors involved in body weight regulation[58] and these findings were reproduced in animal models.[59] Most antidiabetics, including insulin, sulfonylureas and thiazolidinediones also promote adiposity, especially the newer thiazolidinediones, which promote adipocyte proliferation.[60] Beta-blockers induce a mean weight gain of approximately 1.2 kg.[61] Data are less consistent for oral contraceptives, but one study estimated a mean weight gain of approximately 5 kg at 2 years.[62] Antihistamines also appear to induce weight gain, with more potent antihistamines producing greater weight gain.[63] Human immunodeficiency virus antiretroviral drugs and protease inhibitors also produce weight gain and increased abdominal adiposity.[64]

Evidence that use of such pharmaceuticals has increased
Most pharmaceuticals described above were introduced or had their use dramatically increased in the past three decades. In the past 30 years, outpatient prescriptions for atypical antipsychotic medications have increased from essentially zero to be nearly 70% of the prescriptions to this large patient population.[65,66] Oral antidiabetic prescriptions increased more than twofold from 1990 to 2001.[67] Similar increases were also observed for use of anticonvulsants[68] and antihypertensives.[69] Human immunodeficiency virus therapies were only introduced in the past couple of decades.

Additional Explanation 6: changes in distribution of ethnicity and age

Evidence that some age and ethnic groups have higher prevalence of obesity than others
Compared with young European Americans, middle-aged adults, African Americans (when comparing women only) and Hispanic Americans have a markedly higher obesity prevalence.[1]

Evidence that those age and ethnic groups have increased in relative frequency
As a proportion of US adults, the Hispanic-American population increased from less than 5% in 1970 to approximately 13% in 2000.[70,71] Similarly, from 1970 to 2000, the proportion of the total US adult population aged 35–44 and 45–54 years increased by 43 and 18%, respectively.[71] Given that these groups have higher than average obesity rates, it is likely that these demographic changes in the population are contributing to the increased prevalence of obesity in at least a small way.

Additional Explanation 7: increasing gravida age

Evidence that greater gravida age increases risk of offspring obesity
Wilkinson *et al*.[72] studied obese British children and found that a common risk factor was having an elderly mother. Patterson *et al*.[73] studied girls aged 9–10 years and found that the odds of obesity increased 14.4% for every 5-year increment in maternal age. Biological data support these findings. Symonds *et al*.[74] observed a correlation between maternal age and fat deposition in sheep, in part related to uncoupling protein levels. This is in part related to an accelerated loss of the brown adipose uncoupling protein 1 levels in the offspring of adult primiparous mothers after birth, which may act to increase white adipose tissue deposition in later life.[74]

Evidence that gravida age is increasing
Gravida age is increasing globally,[75,76] rising in mean by 1.4 years in the United Kingdom between 1984 and 1994[75] and in median by 2 years in Canada from 1981 to 1987.[76] Mean age at first birth has increased by 2.6 years among US mothers since 1970.[77] Given Patterson *et al*.'s[73] finding above, these increases in maternal age might produce a clinically meaningful ~7% increase in the odds of obesity.

Additional Explanation 8: intrauterine and intergenerational effects

Some influences on obesity may occur *in utero* or even two generations back when oocytes are formed in the grandmother.[78] These may occur partly through epigenetic (e.g., methylation) events as evidenced by the fact that cloned mice tend to be obese yet do not pass on this obesity to their offspring.[79] Thus, the increases in obesity we see today may well be due, in part, to environmental changes that affected prior generations. Obesity, which began increasing at least a century ago,[2] may perpetuate its own increase through a fetally driven positive feedback loop. Specifically, maternal obesity and resulting diabetes during gestation and lactation may promote the same conditions in subsequent generations.[80]

Animal studies testing the fetal origin hypothesis provide support.[81–83] In one study, offspring from parent rats fed high- and low-fat diets were fed a high-fat diet. Not only were body weight and abdominal adiposity increased in the offspring of high-fat-fed parents but also the effect remained significant over three generations.[81,84] Similarly, overfeeding first-generation female pups produced heavier pups as compared with a control group and effects persisted for two subsequent generations.[84] In humans, birth weight positively correlates with adult BMI. However, as Allison *et al*.[85] showed, barring extreme variations, this association seems to reflect common genetic influences on birth weight

and adult BMI rather than an intrauterine environment that affects both birth weight and adult obesity. Nevertheless, there may be intrauterine effects on adult BMI that are not manifested in high birth weight. New evidence suggests that low birth weight and/or the rapid catch-up growth that often follows, may be a risk factor for later obesity and its life-shortening sequelae.[86] It is then noteworthy that the incidence of low birth weight in the United States has increased. According to Hamilton *et al.*,[87] low birth weight increased to 7.8% for 2002, the highest in more than three decades; the rate of low birth weight had declined in the 1970s and early 1980s, but has increased since the mid-1980s. Furthermore, mothers who were themselves low-birth weight infants are at increased risk for gestational diabetes,[88] which, in turn, places their offspring at increased obesity risk.[89]

Thus, it is possible that the extremes of energy imbalance *in utero* (overfeeding and low birth weight) may contribute to obesity. We may now be seeing the transgenerational obesogenic effects of environmental changes initiated one or more generations ago. Forebodingly, obesity's prevalence could increase further if children of the current generation's overweight or obese parents are thereby predisposed further still.

Additional Explanation 9: greater BMI is associated with greater reproductive fitness yielding selection for obesity-predisposing genotypes

Reproductive fitness can be defined as one's capacity to pass on one's DNA. Body mass index-associated reproductive fitness (viz. natural selection) would increase obesity prevalence if BMI has a genetic component (i.e., is heritable) and if individuals genetically predisposed toward higher BMIs reproduce at a higher rate than do individuals genetically predisposed toward lower BMIs.

Proposition A: BMI has a genetic component
That BMI (or adiposity) has a heritable component is well supported by animal breeding studies and human twin, family and adoption studies[90] with an estimated heritability of approximately 65%.[91]

Proposition B: individuals with genetic predisposition toward greater adiposity are reproducing at a higher rate than are individuals with a predisposition toward lesser adiposity
Number of offspring is positively correlated with BMI among women.[92] One might assume that this is because childbearing or child rearing leads to weight gain. Although this is plausible, other mechanisms may be contributing to this correlation. Specifically, mild-to-moderate (but not severe) phenotypic obesity and/or a genotypic predisposition to obesity may increase fecundity relative to phenotypic thinness and/or a genetic predisposition to thinness because (1) obesity (at least in women) leads to socioeconomic falling[93,] which, in turn, is associated with producing more offspring;[94] (2) leanness beyond a certain point impairs fertility in women[95] and (3) other biological, social or economic factors may induce a positive correlation between genetic predisposition to obesity and fecundity. Indeed, evidence shows that the direction of causation may also be from obesity predisposition to fecundity, and not only the reverse. First, although true that high BMI ($>25\,kg/m^2$) is associated with reduced sperm concentration and total sperm count, so too is low BMI ($<20\,kg/m^2$) and the reduction is greater among men with low BMI,[96] there is an association between parent adiposity and number of offspring for both fathers and mothers.[97] Although this does not rule out that child rearing leads to obesity, the correlation among fathers obviously cannot be ascribed to the effects of childbearing. Second, at least one study showed that higher BMI among parents before producing offspring is associated with subsequent offspring number.[97] Finally, animal studies are supportive: in cattle, calving rate and adiposity have a positive genetic correlation[98] and in male rhesus monkeys, adiposity is positively correlated with siring rate.[99]

Additional Explanation 10: assortative mating and floor effects

Assortative mating is a pattern of non-random mating that we will use to refer to positive assortment in which the probability that two individuals mate is positively related to their degree of phenotypic similarity. Assortative mating increases genetic variance in a population, even though it does not affect allele frequencies (it does affect genotype frequencies). Three propositions imply that assortative mating is contributing to increased obesity prevalence:[100,101] (1) human adiposity variations have a genetic component; (2) the adiposity threshold for defining obesity was historically above the population median and (3) humans assortatively mate for adiposity. Moreover, if factors are present that prevent most people from becoming extremely thin (i.e., floor effects), then the population distribution of adiposity will become increasingly positively skewed, further increasing the population mean. The extent of assortative mating does not need to have increased over time, for it to have contributed to increasing prevalence of obesity over time.

Evidence that human adiposity variations have a genetic component
This was discussed in the context of Additional Explanation 9.

The threshold for defining obesity was historically above the population median
The threshold for defining obesity is currently a BMI of $30\,kg/m^2$. This is above the present and historical median BMI.[1]

Humans assortatively mate for adiposity
Extensive research shows that for BMI and other adiposity indicators, the spousal correlation is small (~0.15) but clearly statistically significant and cannot be attributed to the effects of cohabitation.[102] This combined evidence strongly suggests that assortative mating has contributed to the epidemic.[100,101] Finally, there are clear floor effects on BMI[103] that have likely accentuated these effects.

Putting it all together: interconnections

Having laid out several of these possible contributing factors, it is interesting to consider what their relative importance may be and whether there are interconnections among these putative causal variables. With respect to their relative importance, importance can be judged in multiple ways. For example, one could judge importance in terms of the amount of variance in BMI explained, the magnitude of the mean increase in BMI, a population attributable fraction or some other measure of effect. Unfortunately, we do not believe we are currently at the point where we can confidently say what the effect size metrics are for each of these putatively causal variables and therefore cannot confidently evaluate their relative importance on these metrics. Another way to consider the importance of variables is their potential modifiability. It is unlikely that anyone would suggest that we should have more people take up smoking as a way of controlling body weight. Therefore, further consideration of the effects of smoking cessation on population increases on BMI may be less important than consideration of other factors that we might be more willing or able to modify. In this regard, factors such as sleep reduction and increased use of heating and air-conditioning might be things that are easily modifiable and for which modifications in the direction that would hypothetically reduce obesity levels would also have added benefits (e.g., a more healthy and alert population and less use of fossil fuels). Thus, these types of putative contributing factors may be more important in terms of meriting more attention.

It is also noteworthy that there may be interconnections among these putative contributing factors. For example, Additional Explanation 6 specifies that the average age of the US adult population has increased relative to the average age of that population several decades ago. Even if the rates of reproduction within an age category remain constant, this would not only result in an older adult population who are more likely to be obese solely by virtue of their own age but would also result in increasing gravida age on average (Additional Explanation 7), which may lead to more obesity among offspring. Moreover, the greater obesity among the parental generation, owing in part to increasing age, may also predispose to greater obesity among the offspring generation as articulated in Additional Explanation 8. Similarly, it is possible that the effects of assortative mating, as discussed in Additional Explanation 10, may be accentuated by all other factors. That is, it is possible that the influence of assortative mating is quite modest when most people lie within some intermediate range of BMI with very few people being severely obese. However, as larger proportions of the population become severely obese as a result of the influence of other factors, it may be that there is a greater pattern of intermating among these severely obese individuals, which may then further accelerate the increase in obesity levels in subsequent generations. There may yet be additional connections among these factors that remain to be explored.

Discussion

The evidence for the putative roles of the 10 Additional Explanations in the epidemic is compelling and in most cases consists of the concurrence of ecological correlations, epidemiologic study results, model organism studies, and strong theoretical or plausible mechanisms of action models. Nevertheless, we do not claim that all of the Additional Explanations definitively are contributors, but only that they are as plausibly so as are the Big Two and deserve more attention and study.

Although the effect of any one factor may be small, the combined effects may be consequential. Moreover, the Additional Explanations we consider do not exhaust the possibilities. Other factors potentially involved in the epidemic with varying degrees of evidential support include an epidemic of adenovirus-36,[104] increases in childhood depression,[105] less calcium (or dairy) consumption[106] and hormones in agricultural species.[107] In trying to reduce obesity levels, we consider only factors that have changed over time and potentially contributed to the epidemic. Other factors such as shift work[108,109] and not breastfeeding[110] can contribute to obesity; decreasing them may alleviate the epidemic, even though they may not have contributed to it, because their rates have not increased in the past 30 years.[111,112] Of course, as we consider any environmental factor, it is important to remain cognizant that such factors act in concert with individual genetic susceptibilities.[113]

Bray and Champagne[114] have recently published a review of five environmental agents that they found disturb energy balance and cause obesity in susceptible hosts. Although they offer three available strategies for combating the epidemic (nutrition education, regulation of serving size and food labels, and modification to the food system), their suggested measures target the Big Two and not the drugs, chemicals, viruses or toxins that they have implicated as contributing factors. If the Additional Explanations we have offered are probable contributors to the epidemic as we believe, then additional research is warranted to evaluate how much they actually contribute, their mechanisms of action, their interaction effects and how they may be

countermanded. Although we are not suggesting in this paper that one discount the potential effects of the Big Two, if Additional Explanations are veracious, the expectations for the likely public health impact of programs that only target the Big Two might be tempered. Public health practitioners and clinicians may need to address a broader range of influential factors to more adequately address the epidemic.

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References

1 Hedley AA, Ogden CL, Johnson CL, Carroll MD, Curtin LR, Flegal KM. Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *JAMA* 2004; **291**: 2847–2850.
2 Heimburger DC, Allison DB, Goran MI, Heini AF, Hensrud DD, Hunter GR *et al*. A festschrift for Roland L Weinsier: nutrition scientist, educator, and clinician. *Obes Res* 2003; **11**: 1246–1262.
3 Swinburn B, Egger G. The runaway weight gain train: too many accelerators, not enough brakes. *BMJ* 2004; **329**: 736–769.
4 Gabbard C. The need for quality physical education. *J Sch Nurs* 2001; **17**: 73–75.
5 Sothern MS. Obesity prevention in children: physical activity and nutrition. *Nutrition* 2004; **20**: 704–708.
6 Matthiessen J, Fagt S, Biltoft-Jensen A, Beck AM, Ovesen L. Size makes a difference. *Public Health Nutr* 2003; **6**: 65–72.
7 Ebbeling CB, Sinclair KB, Pereira MA, Garcia-Lago E, Feldman HA, Ludwig DS. Compensation for energy intake from fast food among overweight and lean adolescents. *JAMA* 2004; **291**: 2828–2833.
8 Rogers JH. Living on the fat of the land: how to have your burger and sue it too. *Washington Univ Law Q* 2003; **81**: 859–884.
9 Bray GA. The epidemic of obesity and changes in food intake: the fluoride hypothesis. *Physiol Behav* 2004; **82**: 115–121.
10 Morgenstern H. Ecologic studies in epidemiology: concepts, principles, and methods. *Annu Rev Public Health* 1995; **16**: 61–81.
11 US Food and Drug Administration. Redbook 2000: Toxicological Principles for the Safety Assessment of Food Ingredients. Available at: http://vm.cfsan.fda.gov/~redbook/red-vib.html Accessed March 3, 2005.
12 Caballero B, Clay T, Davis SM, Ethelbah B, Rock BH, Lohman T, *et al.*, Pathways Study Research Group. Pathways: a school-based, randomized controlled trial for the prevention of obesity in American Indian schoolchildren. *Am J Clin Nutr* 2003; **78**: 1030–1038.
13 Burdette HL, Whitaker RC. Neighborhood playgrounds, fast food restaurants, and crime: relationships to overweight in low-income preschool children. *Prev Med* 2004; **38**: 57–63.
14 Berkey CS, Rockett HR, Field AE, Gillman MW, Colditz GA. Sugar-added beverages and adolescent weight change. *Obes Res* 2004; **12**: 778–788.
15 Field AE, Austin SB, Gillman MW, Rosner B, Rockett HR, Colditz GA. Snack food intake does not predict weight change among children and adolescents. *Int J Obes Relat Metab Disord* 2004; **28**: 1210–1216.
16 Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet* 2001; **357**: 505–508.
17 Newby PK, Peterson KE, Berkey CS, Leppert J, Willett WC, Colditz GA. Beverage consumption is not associated with changes in weight and body mass index among low-income preschool children in North Dakota. *J Am Diet Assoc* 2004; **104**: 1086–1094.
18 Marshall SJ, Biddle SJ, Gorely T, Cameron N, Murdey I. Relationships between media use, body fatness and physical activity in children and youth: a meta-analysis. *Int J Obes Relat Metab Disord* 2004; **28**: 1238–1246.
19 Rolls BJ. The supersizing of America: portion size and the obesity epidemic. *Nutr Today* 2003; **38**: 42–53.
20 von Kries R, Toschke AM, Wurmser H, Sauerwald T, Koletzko B. Reduced risk for overweight and obesity in 5- and 6-years-old children by duration of sleep – a cross-sectional study. *Int J Obes Relat Metab Disord* 2002; **26**: 710–716.
21 Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB. Inadequate sleep as a risk factor for obesity: analysis of the NHANES I. *Sleep* 2005; **28**: 1289–1296.
22 Everson CA. Functional consequences of sustained sleep deprivation in the rat. *Behav Brain Res* 1995; **69**: 43–54.
23 Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet* 1999; **354**: 1435–1439.
24 Spiegel K, Leproult R, L'hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab* 2004; **89**: 5762–5771.
25 Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PloS Med* 2004; **1**: e62.
26 Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med* 2004; **141**: 846–850.
27 Bonnet MH, Arand DL. We are chronically sleep deprived. *Sleep* 1995; **18**: 908–911.
28 Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics* 2003; **111**: 302–307.
29 Bitz C, Harder H, Astrup A. A paradoxical diurnal movement pattern in obese subjects with type 2 diabetes: a contributor to impaired appetite and glycemic control? *Diabetes Care* 2005; **28**: 2040–2041.
30 Resta O, Foschino BMP, Bonfitto P, Giliberti T, Depalo A, Pannacciulli N *et al*. Low sleep quality and daytime sleepiness in obese patients without obstructive sleep apnoea syndrome. *J Intern Med* 2003; **253**: 536–543.
31 Wade GN, Gray JM, Bartness TJ. Gonadal influences on adiposity. *Int J Obes* 1985; **9** (Suppl 1): 83–92.
32 Haarbo J, Marslew U, Gotfredsen A, Christiansen C. Postmenopausal hormone replacement therapy prevents central fat distribution. *Metabolism* 1991; **40**: 1323–1326.
33 Heine PA, Taylor JA, Iwamoto GA, Lubahn DB, Cooke PS. Increased adipose tissue in male and female estrogen receptor-alpha knockout mice. *Proc Natl Acad Sci USA* 2000; **97**: 12729–12734.
34 Kanayama T, Kobayashi N, Mamiya S, Nakanishi T, Nishikawa J. Organotin compounds promote adipocyte differentiation as agonists of the peroxisome proliferator-activated receptor γ/retinoid X receptor pathway. *Mol Pharmacol* 2005; **67**: 766–774.

35 Uzumcu M, Suzuki H, Skinner M. Effect of the anti-androgenic endocrine disruptor vinclozolin on embryonic testis cord formation and postnatal testis development and function. *Reprod Toxicol* 2004; **18**: 765–774.
36 Sohoni P, Sumpter JP. Several environmental oestrogens are also anti-androgens. *J Endocrinol* 1998; **158**: 327–339.
37 Woodhouse AJ, Cooke GM. Suppression of aromatase activity *in vitro* by PCBs 28 and 105 and Aroclor 1221. *Toxicol Lett* 2004; **152**: 91–100.
38 Pelletier C, Imbeault P, Tremblay A. Energy balance and pollution by organochlorines and polychlorinated biphenyls. *Obes Rev* 2003; **4**: 17–24.
39 Noren K, Meironyte D. Certain organochlorine and organobromine contaminants in Swedish human milk in perspective of past 20–30 years. *Chemosphere* 2000; **40**: 1111–1123.
40 Nilsson R. Endocrine modulators in the food chain and environment. *Toxicol Pathol* 2000; **28**: 420–431.
41 Westerterp-Plantenga MS, van Marken Lichtenbelt WD, Cilissen C, Top S. Energy metabolism in women during short exposure to the thermoneutral zone. *Physiol Behav* 2002; **75**: 227–235.
42 Saxton C. Effects of severe heat stress on respiration and metabolic rate in resting man. *Aviat Space Environ Med* 1981; **52**: 281–286.
43 Mader TL. Environmental stress in confined beef cattle. *J Anim Sci* 2003; **81**: E110–E119.
44 Collin A, van Milgen J, Dubois S, Noblet J. Effect of high temperature on feeding behaviour and heat production in group-housed young pigs. *Br J Nutr* 2001; **86**: 63–70.
45 Herman CP. Effects of heat on appetite. In: Marriott BM (ed). *Nutritional Needs in Hot Environments: Applications for Military Personnel in Field Operations*. National Academy Press: Washington, DC, 1993, pp 187–214.
46 EHCS 2000. *Housing Research Summary: English House Condition Survey 1996: Energy Report (No. 120)*. Office of the Deputy Prime Minister, The Stationary Office: UK.
47 Understanding comfort, behavior, and productivity. Available at: http://www.esource.com/public/pdf/Heating.pdf (accessed March 3, 2005).
48 E Source space heating atlas. Available at: http://www.esource.com/public/products/atlas_heating.asp (accessed March 3, 2005).
49 Type of air-conditioning equipment by census region and survey year. Available at: http://www.eia.doe.gov/emeu/consumptionbriefs/recs/actrends/recs_ac_trends_table2.html (accessed March 3, 2005).
50 Flegal KM, Troiano RP, Pamuk ER, Kuczmarski RJ, Campbell SM. The influence of smoking cessation on the prevalence of overweight in the United States. *N Engl J Med* 1995; **333**: 1165–1170.
51 Filozof C, Fernandez Pinilla MC, Fernandez-Cruz A. smoking cessation and weight gain. *Obes Rev* 2004; **5**: 95–103.
52 Jessen AB, Buemann B, Toubro S, Skovgaard IM, Astrup A. The appetite-suppressant effect of nicotine is enhanced by caffeine. *Diab Obes Metab* 2005; **7**: 327–333.
53 Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 2002. *Morb Mortal Wkly Rep* 2004; **53**: 427–431.
54 Fava M. Weight gain and antidepressants. *J Clin Psychiatry* 2000; **61** (Suppl 11): 37–41.
55 Garland EJ, Remick RA, Zis AP. Weight gain with antidepressants and lithium. *J Clin Psychopharmacol* 1988; **8**: 323–330.
56 Sussman N, Ginsberg DL, Bikoff J. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J Clin Psychiatry* 2001; **62**: 256–260.
57 Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC *et al*. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156**: 1686–1696.
58 Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry* 2001; **62** (Suppl 7): 22–31.
59 Cope MB, Nagy TR, Fernandez JR, Geary N, Casey DE, Allison DB. Antipsychotic drug–induced weight gain: development of an animal model. *Int J Obes Relat Metab Disord* 2005; **29**: 607–614.
60 Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. *Am J Med* 2003; **115** (Suppl 8A): 42S–48S.
61 Sharma AM, Pischon T, Hardt S, Kunz I, Luft FC *et al*. Hypothesis: beta-adrenergic receptor blockers and weight gain. A systematic analysis. *Hypertension* 2001; **37**: 250–254.
62 Espey E, Steinhart J, Ogburn T, Qualls C. Depo-provera associated with weight gain in Navajo women. *Contraception* 2000; **62**: 55–58.
63 Aronne LJ. Drug-induced weight gain: non-CNS medications. In: Aronne LJ (ed). *A Practical Guide to Drug-induced Weight Gain*. McGraw-Hill: Minneapolis, MN, 2002. pp 77–91.
64 Stricker RB, Goldberg B. Weight gain associated with protease inhibitor therapy in HIV-infected patients. *Res Virol* 1998; **149**: 123–126.
65 Daumit GL, Crum RM, Guallar E, Rowe RN, Primm AB, Steinwachs EM *et al*. Outpatient prescriptions for atypical antipsychotics for African Americans, Hispanics and Whites in the United States. *JAMA* 2003; **60**: 121–128.
66 Hermann RC, Yang D, Ettner SL, Marcus SC, Yoon C, Abraham M. Prescription of antipsychotic drugs by office-based physicians in the United States, 1989–1997. *Psychiatr Serv* 2002; **53**: 425–430.
67 Wysowski DK, Armstrong G, Governale L. Rapid increase in the use of oral antidiabetic drugs in the United States, 1990–2001. *Diabetes Care* 2003; **26**: 1852–1855.
68 Citrome L, Jaffe A, Levine J, Allingham B. Use of mood stabilizers among patients with schizophrenia, 1994–2001. *Psychiatr Serv* 2002; **53**: 1212.
69 Psaty BM, Manolio TA, Smith NL, Heckbert SR, Gottdiener JS, Burke GL *et al*. Time trends in high blood pressure control and use of antihypertensive medications in older adults. *Arch Intern Med* 2002; **162**: 2325–2332.
70 Race and Hispanic origin 1790–1990. Available at: http://www.census.gov/population/documentation/twps0056/tab01.pdf (accessed March 15, 2005).
71 The Hispanic population 2000. Available at: http://www.census.gov/prod/2001pubs/c2kbr01-3.pdf (accessed March 15, 2005).
72 Wilkinson PW, Parkin JM, Pearlson J, Philips PR, Sykes P. Obesity in childhood: a community study in Newcastle upon Tyne. *Lancet* 1977; **1**: 350–352.
73 Patterson ML, Stern S, Crawford PB, McMahon RP, Similo SL, Schreiber GB *et al*. Sociodemographic factors and obesity in preadolescent black and white girls: NHLBI's Growth and Health Study. *J Natl Med Assoc* 1997; **89**: 594–600.
74 Symonds ME, Pearce S, Bispham J, Gardner DS, Stephenson T. Timing of nutrient restriction and programming of fetal adipose tissue development. *Proc Nutr Soc* 2004; **63**: 397–403.
75 Armitage B, Babb P. Population review: (4). Trends in fertility. *Popul Trends* 1996; **84**: 7–13.
76 Wadhera S. Trends in birth and fertility rates, Canada, 1921–1987. *Health Rep* 1989; **1**: 211–223.
77 Mathews TJ, Hamilton BE. Mean age of mother, 1970–2000. *Natl Vital Stat Rep* 2002; **51**: 1–13.
78 Finch CE, Loehlin JC. Environmental influences that may precede fertilization: a first examination of the prezygotic hypothesis from maternal age influences on twins. *Behav Genet* 1998; **28**: 101–106.
79 Inui A. Obesity – a chronic health problem in cloned mice? *Trends Pharmacol Sci* 2003; **24**: 77–80.
80 Levin B, Govek E. Gestational obesity accentuates obesity in obesity-prone progeny. *Am J Physiol* 1998; **275**: R1374–R1379.
81 Wu Q, Mizushima Y, Komiya M, Matsuo T, Suzuki M. Body fat accumulation in the male offspring of rats fed high-fat diet. *J Clin Biochem Nutr* 1998; **25**: 71–79.

82 Wu Q, Mizushima Y, Komiya M, Matsuo T, Suzuki M. The effects of high-fat diet feeding over generations on body fat accumulation with lipoprotein lipase and leptin in rat adipose tissues. *Asia Pacific J Clin Nutr* 1999; **8**: 46–52.
83 Lim K, Shimomura Y, Suzuky M. Effects of high-fat diet feeding over generations on body fat accumulation. In: Romsos DR, Himms-Hagen J, Suzuky, M (eds) *Obesity: Dietary Factors and Control*. Karger, Basel: Switzerland, 1991, pp 181–190.
84 Diaz J, Taylor EM. Abnormally high nourishment during sensitive periods results in body weight changes across generations. *Obes Res* 1998; **6**: 368–374.
85 Allison DB, Paultre F, Heymsfield SB, Pi-Sunyer FX. Is the intrauterine period really a critical period for the development of adiposity? *Int J Obes Relat Metab Disord* 1995; **19**: 397–402.
86 Ozanne SE, Hales CN. Lifespan: catch-up growth and obesity in male mice. *Nature* 2004; **427**: 411–412.
87 Hamilton BE, Martin JA, Sutton PD. Births: preliminary data for 2003. *Natl Vital Stat Rep* 2004; **53**: 1–17.
88 Bo S, Marchisio B, Volpiano M, Menato G, Pagano G. Maternal low birth weight and gestational hyperglycemia. *Gynecol Endocrinol* 2003; **17**: 133–136.
89 Silverman BL, Rizzo TA, Cho NH, Metzger BE. Long-term effects of the intrauterine environment. The Northwestern University Diabetes in Pregnancy Center. *Diabetes Care* 1998; **21**: B142–B149.
90 Allison DB, Pietrobelli A, Faith MS, Fontaine KR, Gropp E, Fernández JR. Genetic influences on obesity. In: Eckel R (ed). *Obesity: Mechanisms & Clinical Management*. Elsevier: New York, 2003, pp 1–74.
91 Segal NL, Allison DB. Twins and virtual twins: bases of relative body weight revisited. *Int J Obes Relat Metab Disord* 2002; **26**: 437–441.
92 Weng HH, Bastion LA, Taylor DH, Moser BK, Ostbye T. Number of children associated with obesity in middle-aged women and men: results from the health and retirement study. *J Womens Health* 2004; **13**: 85–91.
93 Lipowicz A. Effect of husbands' education on fatness of wives. *Am J Hum Biol* 2003; **15**: 1–7.
94 Salihu HM, Kinniburgh BA, Aliyu MH, Kirby RS, Alexander GR. Racial disparity in stillbirth among singleton, twin and triplet gestations in the United States. *Obstet Gynecol* 2004; **104**: 734–740.
95 Frisch RE. Body fat, menarche, fitness and fertility. *Hum Reprod* 1987; **2**: 521–533.
96 Jensen TK, Andersson AM, Jorgensen N, Andersen AG, Carlsen E, Petersen JH *et al*. Body mass index in relation to semen quality and reproductive hormones among 1558 Danish men. *Fertil Steril* 2004; **82**: 863–870.
97 Ellis L, Haman D. Population increases in obesity appear to be partly due to genetics. *J Biosoc Sci* 2004; **36**: 547–559.
98 Splan RK, Cundiff LV, Van Vleck LD. Genetic correlations between male carcass and female growth and reproductive traits in beef cattle. Available at: http://elib.tiho-hannover.de/publications/6wcgalp/papers/23274.pdf (accessed March 4, 2005).
99 Bercovitch FB, Nurnberg P. Socioendocrine and morphological correlates of paternity in rhesus macaques (*Macaca mulatta*). *J Reprod Fertil* 1996; **107**: 59–68.
100 Hebebrand J, Wulftange H, Goerg T, Ziegler A, Hinney A, Barth N *et al*. Epidemic obesity: are genetic factors involved via increased rates of assortative mating? *Int J Obes Relat Metab Disord* 2000; **24**: 345–353.
101 Katzmarzyk PT, Hebebrand J, Bouchard C. Spousal resemblance in the Canadian population: implications for the obesity epidemic. *Int J Obes Relat Metab Disord* 2002; **26**: 241–246.
102 Katzmarzyk PT, Perusse L, Rao DC, Bouchard C. Spousal resemblance and risk of 7-year increases in obesity and central adiposity in the Canadian population. *Obes Res* 1999; **7**: 545–551.
103 Henry CJK. Variability in adult body size: uses in defining the limits of human survival. In: Ulijaszek SJ, Mascie-Taylor CGN (eds). *Anthropometry: The Individual and the Population*. Cambridge University Press: New York, 1994, pp 117–129.
104 Atkinson RL, Dhurandhar NV, Allison DB, Bowen RL, Israel BA, Albu JB *et al*. Humanadenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. *Int J Obes* 2005; **29**: 281–286.
105 Pine DS, Goldstein RB, Wolk S, Weissman MM. The association between childhood depression and adulthood body mass index. *Pediatrics* 2001; **107**: 1049–1056.
106 Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dairy acceleration of weight and fat loss during energy restriction in obese adults. *Obes Res* 2004; **12**: 582–590.
107 Mayfield R Hormones in meat—what you should know! News from Dr. Robin. You Can Feel Good!, No. 6, April 22, 2003. Available at: http://www.drrobinmayfield.com/newsletters/newsletter-6.html (accessed March 4, 2005).
108 Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N *et al*. Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. *Int J Obes Relat Metab Disord* 2003; **27**: 1353–1358.
109 Kivimaeki M, Kuisma P, Virtanen M, Elovainio M. Does shift work lead to poorer health habits? A comparison between women who had always done shift work with those who had never done shift work. *Work Stress* 2001; **15**: 3–13.
110 Arenz S, Ruckerl R, Koletzko B, von Kries R. Breast-feeding and childhood obesity – a systematic review. *Int J Obes Relat Metab Disord* 2004; **28**: 1247–1256.
111 Hamermesh DS. The timing of work over time. *Econ J* 1999; **109**, Available at: http://www.res.org.uk/journals/abstracts.asp?ref=0013-0133&vid=109&iid=452&aid=390 (accessed March 4, 2005).
112 Breastfeeding by mothers 15–44 years of age by year of baby's birth, according to selected characteristics of mother: United States, average annual 1972–1974 to 1993–1994. Available at: http://www.cdc.gov/nchs/data/hus/tables/2003/03hus018.pdf (accessed March 4, 2005).
113 Friedman JM. A war on obesity, not the obese. *Science* 2003; **299**: 856–858.
114 Bray GA, Champagne CM. Beyond energy balance: there is more to obesity than kilocalories. *J Am Diet Assoc* 2005; **105** (Suppl 1): S17–S23.
115 Middleton N, Gunnell D, Whitley E, Dorling D, Frankel S. Secular trends in antidepressant prescribing in the UK, 1975–1998. *J Public Health Med* 2001; **23**: 262–267.