

RESEARCH ARTICLE

Microevolutionary hypothesis of the obesity epidemic

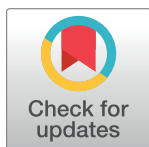
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Abstract

The obesity epidemic represents potentially the largest phenotypic change in *Homo sapiens* since the origin of the species. Despite obesity's high heritability, it is generally presumed a change in the gene pool could not have caused the obesity epidemic. Here we advance the hypothesis that a rapid change in the obesogenic gene pool has occurred second to the introduction of modern obstetrics dramatically altering evolutionary pressures on obesity—the microevolutionary hypothesis of the obesity epidemic. Obesity is known to increase childbirth-related mortality several fold. Prior to modern obstetrics, childbirth-related mortality occurred in over 10% of women in their lifetime. After modern obstetrics, this mortality reduced to a fraction of a percent, thereby lifting a strong negative selection pressure. Regression analysis of data for ~ 190 countries was carried out to examine associations between 1990 lifetime maternal death rates (LMDR) and current obesity rates. Multivariate regression showed LMDR correlated more strongly with national obesity rates than GDP, calorie intake and physical inactivity. Analyses controlling for confounders via partial correlation show that LMDR explains approximately 11% of the variability of obesity rate between nations. For nations with LMDR above the median (>0.45%), LMDR explains 33% of obesity variance, while calorie intake, GDP and physical inactivity show no association with obesity in these nations. The microevolutionary hypothesis offers a parsimonious explanation of the global nature of the obesity epidemic.



OPEN ACCESS

Citation: Fraiman J, Bayer S, Henneberg M (2024) Microevolutionary hypothesis of the obesity epidemic. PLoS ONE 19(8): e0305255. <https://doi.org/10.1371/journal.pone.0305255>

Editor: Mithun Sikdar, Anthropological Survey of India, Government of India, INDIA

Received: January 2, 2024

Accepted: May 27, 2024

Published: August 7, 2024

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Data Availability Statement: All data used in this study has been made public and can be accessed at: <https://doi.org/10.5281/zenodo.10058731>.

Funding: The author(s) received no specific funding for this work.

Competing interests: No authors have competing interests.

Significance statement

Humans underwent a rapid increase in obesity in the 20th century, and existing explanations for this trend are unsatisfactory. Here we present evidence that increases in obesity may be in large part attributable to microevolutionary changes brought about by dramatic reduction of childbirth mortality with the introduction of modern obstetrics. Given the higher relative risk of childbirth in women with obesity, obstetrics removed a strong negative selection pressure against obesity. This alteration would result in a rapid population-wide rise in obesity-

promoting alleles. A cross-country analysis of earlier lifetime maternal death rates and obesity rate today found strong evidence supporting this hypothesis. These findings suggest recent medical intervention influenced the course of human evolution more profoundly than previously realized.

Introduction

Over the last half-century, the world has been experiencing a pandemic less immediately dangerous than the current COVID one, but more insidious—obesity. The increasing rate of obesity appeared to begin in developed countries, but it is now a global health crisis. The diagnostic tool commonly used to detect obesity is Body Mass Index which, despite being fraught with some inadequacies, gives a general picture of increasing adiposity. Obesity, as a pathological state, consists of excessive accumulation of white adipose tissue, not just increase in body mass. It is commonly accepted in the scientific literature, medical community, and population at large that positively altered energy balance—more energy consumed than energy expended—leads to the accumulation of adipose tissue in the body. In addition, a vast quantity of research has been made on the regulation of energy balance and multiple dietary and exercise interventions have been introduced over the last decades to reduce obesity. Alas, to no, or little, avail, since the prevalence of obesity has increased in all nations.

Obesity is a highly heritable trait with twin studies finding heritability between 74% and 90% when only including studies in which zygosity of twins is confirmed [1]. In addition, it is commonly stated that a rapid change in the gene pool cannot have caused the obesity epidemic in such a short period of time [2]. Hence investigation into a genetic basis to the obesity epidemic has been limited. Here we present the hypothesis that a ‘rapid’ change in the obesogenic gene pool has occurred and explains the global nature of the obesity epidemic. We term this the “microevolutionary hypothesis of the obesity epidemic”. Prior to the introduction of modern obstetrics, childbirth deaths of mother and/or child were commonplace and well known to have placed a strong negative selective pressure shaping the course of human evolution. With the introduction of modern obstetrics in the 1930s, childbirth deaths reduced dramatically [3, 4], to a level negligible as an evolutionary pressure. Obesity is a well-known risk factor for maternal and perinatal mortality with the relative risk of death being several fold higher for obese women [5]. This increased relative risk prior to obstetrical care would also have been a high absolute risk and must have exerted a strong negative selection pressure against obesity. Despite this strong selection pressure against obesity, all human populations retain obesity-promoting genes suggesting the existence of a stabilizing component of selection pressure against increased body mass combined with stabilizing pressures against genes causing reductions in body mass such as, for instance anorexia, to maintain “normal” body mass. Modern obstetrics removed the strong selection pressure by childbirth. This would, in a few generations, cause a rapid increase in obesogenic genes in the population. An imbalance in stabilizing selection pressures on obesity-related genes has occurred producing a directional change towards obesity.

Is a rapid change in the gene pool possible?

The widespread belief that the obesity epidemic could not be caused by a rapid change in the gene pool developed prior to the understanding that rapid changes in the gene pool can and do occur. It is now known that these rapid changes occur in a population following a sudden environmental change that dramatically alters evolutionary pressures on a trait with large-standing genetic variation [6]. Obesity is known to have large standing genetic variation, with over 1,000 associated obesity promoting loci estimated [7] each with near negligible

phenotypical penetrance of each allele. This has led to the problem in genome-wide association studies (GWAS) of BMI only identifying about 3% of the alleles of this large standing variation [8]. This phenomenon is referred to as hidden heritability, and it occurs when GWAS studies can identify only a small percentage of the genes controlling a highly heritable phenotype [9]. To understand how this rapid change in gene pool could occur with large standing variation consider if there are 1,000 obesity associated loci and if, hypothetically, each allele increases an individual's BMI by only 0.1kg/m^2 on average, then a shift of just 5% in the allele frequency would increase average BMI in the population by 5kg/m^2 , i.e. from 25 to 30 [10].

Intergenerational GWAS studies have identified rapid gene pool changes in humans that have contributed to changes in phenotype [11]. Global myopia rates have doubled over the past three decades [12]. Twin studies find myopia highly heritable, at 50%-65% [13], GWAS studies have identified myopia-prone genes that explain between 35% and 40% of myopia heritability [13]. A recent GWAS study [11] found in the UK that since 1940 a population-wide increase in multiple myopia alleles has occurred and explains a small, but significant, proportion of the UK myopia epidemic. Given it is plausible that a rapid dramatic environmental change can cause a rapid gene-pool change for traits with large standing genetic variation, such as obesity, next we explore if the change presented by modern obstetrics was dramatic enough to result in a rapid change to the gene pool.

The obstetrical miracle changed the evolutionary pressures on obesity

Prior to modern obstetrics a large percentage of women died during childbirth. For example, multiple African nations in 1990 reported lifetime maternal death rate (LMDR) of over 10%. While the maternal mortality rate (MMR) per birth in these nations was between 1% and 2.6%, their LMDR (the share of women that will die from maternal causes in their lifetime) is a product of their MMR and their relatively high number of childbirths per woman. Most developed nations, prior to modern obstetrics also experienced MMRs of approximately 1% [4]. With the introduction of novel obstetrical care between 1935 and 1945, there was a dramatic and rapid reduction in maternal mortality with many nations having MMRs today below 0.01% approximately a 99% reduction with the large majority of this reduction occurring by 1945 in developed nations [4]. During the same period, perinatal mortality (neonate death in the first month of life) also dropped precipitously [4].

Prior to modern obstetrics the predominant causes of maternal and perinatal mortality included: major hemorrhage, hypertensive disease, specifically pre-eclampsia and eclampsia, infection, asphyxia, and placental abruption [4]. Obesity increases the risk of all the major historical causes of childbirth-related deaths dramatically [5]. Even with modern obstetrics, obesity increases the relative risk of maternal and perinatal mortality by approximately 3–4 fold [5, 14, 15]. Prior to modern obstetrics, obesity likely placed a similar if not greater relative risk on childbirth. Consider how the large relative risk from obesity would produce a strong selection pressure historically while today this selection pressure would be negligible.

A nation with an LMDR of 0.01%, obese women would have an LMDR of approximately 0.04%, this absolute difference in death rate would result in a negligible evolutionary pressure. However, in the pre-obstetric period, obesity would present a high absolute risk, creating a strong negative selection pressure. Sierra Leone in 1990 had an LMDR of nearly 15%; historically the LMDR of all nations was likely in this range presuming they had similar MMRs and fertility rates. Consider a nation prior to modern obstetrics with an LMDR of 15%. In such nations obese women would have an LMDR as high as 60%, given the known relative risk obesity carries with childbirth is four times greater. In addition, prior to modern obstetrics perinatal mortality was approximately 14% of which obesity increases relative risk also by as much as

4 fold, suggesting prior to modern obstetrics an obese woman who survived childbirth, will have as many as 56% of their newborns die in the first month of life. Despite this large disproportionate loss of obesogenic genes due to childbirth deaths, the gene-pool remained stable, suggesting a stabilizing pressure must have existed.

The sudden removal of the negative selection pressure would have led to a rapid increase in obesity prone alleles. Multiple hypotheses have been proposed to identify the potential positive selection pressures on obesity. These have been discussed in detail elsewhere [16, 17]. The microevolutionary hypothesis does not question their potential validity. In addition, a positive pressure for obesity must also have been a floor effect with too many alleles predisposing to low BMI being not sustainable with life, given a BMI of 11 is considered the lowest limit for survival [18]. In addition, low BMI is a well recognized risk factor for infertility, with the risk increasing as BMI decreases [19]. The floor effect alone represents a potential positive stabilizing selection pressure towards higher BMI, while childbirth represented a counter negative selection pressure.

Modern medicine has not removed the evolutionary pressure represented by the floor effect against low BMI. However, the sudden environmental change introduced by modern obstetrics since 1935–1945 did result in the exact conditions required for rapid gene-pool change for a trait like obesity with large standing genetic variation. To conceptualize how this would result in rapid population gene pool change, we consider the absolute mortality risk differences obesity likely produced during childbirth historically. Considering the previously extrapolated historical LMDRs and neonatal mortality rates—if 60% of obese women died during childbirth in their lifetime versus 15%, and of those who survived 56% of their children died versus 14%. Taking these mortality rate differences suggests in every generation obese women produced approximately 50% less offspring than non-obese women. Without a stabilizing pressure this would have resulted in a 50% reduction in obesogenic genes in the population gene pool with each generation, and the population would retain nearly no obesogenic genes. However, obesity rates were likely relatively stable, suggesting a stabilizing positive pressure was simultaneously increasing obesogenic genes in the population, at the same rate they were being removed from the gene pool. This relative increase in obesogenic genes could occur via lower survival or reproduction of individuals with lower BMI, or from higher survival or reproduction for higher BMI individuals for reasons unrelated to childbirth. In either case, a hypothetical scenario in which it is presumed a population's obesogenic gene pool had large standing variation and had been stable with 10% of their gene pool being obesogenic once the negative pressure against obesity is removed with modern obstetrics but the positive pressure remains. In this hypothetical scenario in a single generation the relative frequency of obesogenic genes would rise from 10% to 15% of the obesogenic gene pool. In short, the mutation/selection balance for body mass has been altered by modern obstetrics relaxing selection against increased body mass. This would rapidly result in obesity. Examining in detail the time course of the obesity epidemic can elucidate if this matches when the phenotype changes would be expected to be observed following the introduction of obstetrics.

The timing and pattern of the obesity epidemic

The obesity epidemic is thought to have begun in the 1970s–1980s [20]. However, when examining the timing of obesity by birth cohorts, Komlos and Brabec [21] found in the U.S. BMI began rising quickly in those born after 1945 directly after the introduction of modern obstetrics. This phenomenon has been referred to as an obesity cohort effect with generations born more recently having higher rates of obesity, when compared with older generations, and this phenomenon has been observed in multiple developed nations [22–28]. The population born

after modern obstetrics first reached adulthood in the mid 1960s, but by 1970 they represented less than 10% of the US adult population [29]. While this generational cohort did experience a higher rate of obesity than previous generations in the 1960s, the average adult obesity rate appeared to rise only slightly during this time given their relatively small percentage of the population. By 1980, this age segment grew to represent 50% of the population [29], becoming a significant percent of the adult population and with this the average adult obesity rate began to rise quickly, and the obesity epidemic began.

Direct evidence supporting the microevolutionary hypothesis

The evidence presented so far, while not conclusive, does demonstrate that a rapid change in the obesogenic gene pool is plausible. Given the large standing variation of the trait, the innovations of obstetrics produced the exact environmental change necessary for the timing of the phenomenon to begin occurring in those born after this environmental change. These points should be considered when interpreting obesity genetic studies. With this understanding, multiple studies examining obesity genetics reveal evidence supporting that a rapid change in the gene pool has occurred along with the timing expected by the microevolutionary hypothesis. Twin studies comparing obesity genetic variance by birth cohort consistently identify the additive genetic variance of BMI is increasing in those born after the introduction of modern obstetrics with limited changes in environmental variance [30–32]. Without considering the microevolutionary hypothesis, these consistent findings appeared counter-intuitive given most proposed causes of the obesity epidemic have been believed to be environmental changes, well explained by Reddon *et al.* [32]. “One would presume the emergence of a society characterized by food abundance and physical inactivity may increase the impact of environment (and therefore decrease the impact of genes) in the determination of the obese phenotypes. Counter-intuitively, the proportion of variability in BMI attributable to genetic variation is increased among people born after the establishment of a modern ‘obesogenic’ environment.” This finding is well demonstrated by a Swedish twin study, in which they found additive genetic variance of BMI increased significantly between Swedish twin cohorts born in 1951 versus 1981 from 4.3 to 7.9 [31]. This increasing genetic variance in those born in later birth cohorts was significantly correlated with the increasing obesity rate of the population, while the environmental variance of BMI showed no association with the population obesity rate. This pattern of increased genetic variance for BMI, with limited change in environmental variance is exactly what the microevolutionary hypothesis would predict, a population with wider variation of obesity promoting genes. However, these findings were interpreted presuming a change in the obesogenic gene pool is not possible, and suggested the only reasonable way to explain these results is a gene x environment interaction. While it is true these findings could be explained by a gene and environment interaction (and this also may be occurring), a more parsimonious explanation of these results is that a change in the gene pool has occurred. If environmental change increased BMI via a gene and environment interaction one would predict both genetic variance and environmental variance to be increased, not only heritability.

In addition, several longitudinal GWAS studies have identified direct evidence of increases in several of the obesogenic alleles in generations born after the introduction of modern obstetrics [33–36]. Yet the hidden heritability of obesity and GWAS can only explain a limited percent of the known obesity heritability. Therefore, modern GWAS studies can not demonstrate if these changes are or are not producing a measurable effect on the obesity epidemic. However, the pattern of increasing obesogenic genes does support the plausibility of the microevolutionary hypothesis by itself. For example Rosenquist *et al.* [33] reported the gene pool frequency of the well known obesity promoting allele FTO pre and post 1942. Comparing

the frequency of the obesity prone homozygote (AA) and heterozygote (AT), with the frequency of the obesity protective homozygote (TT) in the birth cohorts born before 1942 finds the frequency of the AA/AT was 63.1% compared with the post 1942 frequency of 66.7%. This increase in frequency of the obesity prone homozygote and heterozygote is statistically significant (Chi squared = 24.17 $P < 0.0001$) (For calculation summary see supplementary data). In addition, Walter *et al.* [34] examined genetic risk score with BMI across different birth cohorts. They reported allele frequency across 4 birth cohorts in those born pre 1924 through those born as late as 1958. Of the 29 SNPs they examined, approximately 10% of the obesity prone alleles significantly increased in frequency in the later birth cohorts among population studied, with no obesogenic SNPs decreasing in frequency.

Budnik and Henneberg [35], found that greater national obesity rates are associated with reduced opportunity for natural selection over the past century. Given their findings they proposed that a portion of the obesity epidemic may have been caused by a reduction in evolutionary pressure leading to a rapid change in the gene pool. A recent GWAS study by Wu *et al.* [36] examined obesity genetic risk score (combines known obesogenic alleles to offer a risk of obesity for an individual), across birth cohorts and infant mortality rate during birth year. The study found the number of obesogenic alleles increasing in cohorts born since the 1930s, and in addition, found this increase in obesogenic alleles correlated with infant mortality. The findings of Wu *et al.* [36] offer evidence suggesting that natural selection has occurred in contemporary humans with childbirth related mortality acting as a selection pressure on BMI, exactly as would be predicted by the microevolutionary hypothesis.

A change in the obesogenic gene pool is not only possible but evidence suggests it may have occurred, the wide-spread belief that the obesity epidemic could not have been caused by a rapid change in the population gene-pool can no longer be presumed. Alternatively despite evidence supporting a rapid change in the gene pool, this genetic evidence alone only demonstrates plausibility, and is not sufficient to demonstrate, changes in the gene pool are the major driving force of the obesity epidemic. While the rise of BMI in any nation is certainly multifactorial, with different obesity drivers having larger influences in various nations, examining how the microevolutionary hypothesis can offer an explanation for the global nature of the obesity epidemic offers a parsimonious mechanism tying together the global trends of increasing BMI across disparate nations.

The microevolutionary hypothesis

A parsimonious explanation for the obesity epidemic. Many factors have been identified to influence obesity such as calorie intake and physical activity in addition to microevolutionary change. Importantly, the microevolutionary hypothesis does not challenge that these factors can also have an influence on obesity. However, these and other proposed factors have been insufficient to explain the global nature of the obesity epidemic. This is why there remains no scientific consensus on the cause of the obesity epidemic [37].

Between 1990 and 2016, obesity rates in every nation increased (ourworldindata.org). During this same time period, approximately 25% of nations had decreased or stable total calorie intakes ([Ourworldindata.org](https://ourworldindata.org)). During this time in these nations with stable or decreased calorie intakes, the median increase in obesity rate was approximately 10%. Conversely, examples exist of nations prior to the obesity epidemic in which calorie intake increased with no effect on obesity rate. For example, Switzerland increased calorie intake 17% from ~ 3,000 kcal per day in 1947 to 3,500 kcal per day in 1961 with a negligible change in obesity rate. Switzerland's calorie intake has oscillated up and down between 3,300 and 3,500 kcal per day between 1975 and 2016 while obesity rates consistently increased from 5% to 20% during this period of

relatively unchanged calorie intake ([Ourworldindata.org](https://ourworldindata.org)). This same pattern of increasing calorie intake prior to the obesity epidemic and stable calorie intake during the obesity epidemic has been observed in several other nations including Germany, Poland, France and Finland ([Ourworldindata.org](https://ourworldindata.org)). In addition, multiple nations have been identified to have increasing obesity rates despite increasing average levels of physical activity [38–40].

The microevolutionary hypothesis helps to explain these counter-intuitive discrepancies, as nations with high childbirth related deaths would have strong stabilizing evolutionary pressure keeping the obesity gene pool constant in these populations (ie, increasing calories would have little effect on obesity given the relatively low number of obesity prone alleles including alleles with gene and environment interactions). Conversely, after modern obstetrics is introduced nations would begin to experience an increase in obesogenic genes which are both environmentally dependent and independent. After the introduction of modern obstetrics the microevolutionary hypothesis would predict obesity rates will rise with or without increasing calorie intake or physical inactivity, but would likely rise faster with increased calorie intake or physical inactivity. However, prior to modern obstetrics calorie intake and physical inactivity rates would have little influence on obesity rates, given the relatively small percent of obesogenic alleles in the population, and of these alleles only a fraction would be obese due to gene and environment interactions.

Hypothesis predictions. Some of the predictions of the microevolutionary hypothesis are difficult to test directly because of the hidden heritability of obesity, and the limitation of GWAS studies. Yet the hypothesis does make several predictions that are directly testable using existing data. Specifically, a nation's earlier lifetime maternal death rate (LMDR) should be inversely associated with a nation's obesity rate today. Earlier LMDR should be able to offer additional explanations of obesity rate over confounding variables known to be associated with increasing obesity rates. The data on LMDR for all nations globally were consistently collected since the year 1990 and varied from 0.01% to 14.97%, with a median of 0.48%. The hypothesis would predict that comparing only nations with LMDR below the median in which all nations have LMDRs that are less than a fraction of a percent, the LMDR should have no association with obesity rates given the variation among LMDRs in these nations would produce a negligible difference between these nations in terms of evolutionary pressure. Alternatively, nations with LMDR above the median offer a wide range of LMDR values (0.48%–14.97%) placing variable evolutionary pressures and in these nations LMDR should be more predictive of obesity rates. Considering the example of Switzerland showing calorie intake changes had no association with obesity, prior to 1961, the hypothesis would predict in nations with LMDR above the median that calorie intake and physical inactivity will have limited association with obesity rate given the relatively lower frequency of environmentally dependent obesogenic alleles in the population. However, calorie intake and physical inactivity are expected to be associated with obesity rate in the nations with LMDR below the median given the frequency of environmentally dependent obesogenic alleles is a higher relative percent of these alleles in the population. A third prediction is that no nation with high maternal mortality rates will have a high obesity rate.

Methods

Data extraction methods

Using ourworldindata.org, data were extracted for each nation for maternal mortality rate (MMR), neonatal mortality, and lifetime maternal death rate (LMDR) (share of women that will die from maternal causes in their lifetime) at the earliest year available for which these data were available. For nearly all nations this year was 1990. For Obesity Rates data were

obtained from 1990 and 2016, GDP per capita in 2019, calorie intake 2017. The national rate of insufficient physical activity was obtained from Guthold *et al.* [41], and antibiotic consumption in 2000 from Girum and Wasie [42].

Data analysis

First, scattergrams of relationships with curvilinear regressions fitted and non-parametric correlations (Spearman's rho) of the variables studied were explored. Then natural logarithms of all data were calculated to bring their distributions closer to the homoscedasticity required for parametric correlations and regression analyses. Parametric correlation coefficients of log transformed variables were compared with non-parametric ones to ensure that parametric relationships were close to actual ones. Next, partial correlation analyses of Pearson moment-product correlations were carried out to stabilize the influence of confounding variables such as GDP, calorie intake and physical inactivity on the relationship between obesity and lifetime maternal death rate. Multivariate regression analyses, using obesity as the dependent variable were conducted to establish the strength and significance of the contribution of different variables to the variation in obesity. SPSS v 27 statistical package was used for these analyses.

The World Health Organization defines high Maternal Mortality Rate (MMR) nations when MMR is above 500 deaths in 100,000 live births, this definition was used for this analysis. MMR rates from 1990 were used, being the earliest year in which the MMR of nearly all nations was recorded. The definition of high obesity rate was obtained from the 2017 Obesity update of the Organization for Economic Cooperation and Development (OECD), which reported across the OECD nations 19.5% of the adult population was obese in 2015 [43]. The obesity rate offered by the OECD nations was used as a conservative threshold to define nations with a high obesity rate as 19.5%. Obesity rates from 2016 were used as this was the most recent information available which included all nations globally.

The frequency of high obesity nations was compared between low MMR nations and high MMR nations. In an attempt to exclude the known association between developed nations and obesity, the analysis was performed in nations defined as developing nations by the United Nations World Economic Situation and Prospects report released in 2017 describing the nations the year prior in 2016 [44]. The same analysis was performed in only low-income nations to help reduce the confounding effect of GDP on obesity. Low income nations included nations defined by the United Nations World Economic Situation and Prospects in 2017 as either low income or low middle income nations.

Results

Fig 1 shows regressions of obesity prevalence rates in 1990 and in 2016 on LMDR in 1990. Regressions are of the same kind—exponential and of the same strength, about 50% of variance in obesity rate in each case is explained by LMDR. Similar regressions of obesity prevalence rates on neonatal mortality 1990 exist, though they are weaker as those on LMDR. Neonatal mortality explains only about 20% of obesity variance (S1 Fig in S1 Text). Since the LMDR and neonatal mortality are strongly correlated ($r = 0.88$) in our dataset, further analysis was limited to LMDR.

Obesity rates among countries in 1990 and in 2016 were strongly correlated (Spearman's "rho" = 0.955, Pearson's moment product $r = 0.969$, $p < 0.001$, $N = 191$), thus further analyses were conducted using only the 2016 obesity rates.

Lifetime maternal death rates of 191 countries correlate strongly, negatively and significantly with those countries' obesity prevalence rates (Table 1). They also correlate significantly with GDP, physical inactivity, caloric consumption and antibiotic use. These variables, that

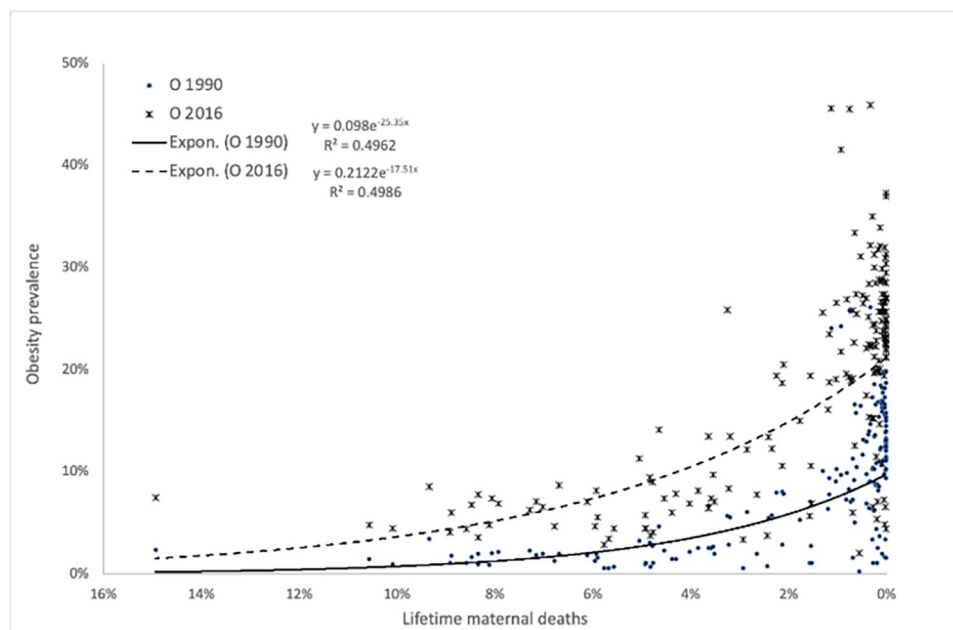


Fig 1. Regressions of obesity rates per country in 1990 and 2016 on LMDR. LMDR, Lifetime maternal death rate in 1990. Please note the strong negative relationship $R = -0.70$ —the lower the LMDR, the greater the obesity prevalence. Strength of the relationship is the same for 1990 as for 2016.

<https://doi.org/10.1371/journal.pone.0305255.g001>

also correlate with obesity rates, were considered confounders and thus kept statistically constant when exploring the correlation between LMDR and obesity in partial correlation analysis finding a moment-product r of -0.336 ($p = <0.001$, $N = 133$) (S1 Table in S1 Text).

When logarithmed obesity prevalence rates are treated as a dependent variable and independent variables are logarithmed LMDR, GDP, calorie intake, insufficient physical activity and antibiotic consumption in the linear multivariate regression analysis (Table 2), LMDR was the most significant of the studied variables. Insufficient physical activity and caloric intake were, as expected, significant, but had lower beta coefficients indicating that their effect size on obesity was less strong than that of LMDR. In a stepwise multivariate regression analysis using probability of F to enter ≤ 0.05 and probability of F to remove ≥ 0.10 only lifetime maternal death rates 1990 and caloric intake 2017 were entered, while the other three confounders were removed. With 2016 obesity rates held as the dependent variable LMDR showed a β

Table 1. Correlations between for all variables studied.

	Obesity 2016	LMDR 1990	Insufficient physical activity	Caloric intake	GDP	Antibiotic consumption
Obesity 2016	1	-0.637***	0.401***	0.534***	0.531***	0.412***
LMDR 1990	-0.638***	1	-0.453***	-0.690***	-0.836***	-0.745
Insufficient phys.activity	0.436***	-0.438***	1	0.370***	0.522***	0.316***
Caloric intake	0.565***	-0.695***	0.332***	1	0.705***	0.500***
GDP	0.503***	-0.844***	0.491***	0.702***	1	0.673***
Antibiotic consumption	0.475***	-0.774***	0.335***	0.521***	0.727***	1

LMDR, Lifetime maternal death rate in 1990

Pearson r (above the diagonal) and nonparametric Spearman's ρ (below the diagonal).

The table shows bivariate correlations between logarithmed values of all the variables. *** $p < 0.001$; Number of countries: 147–191.

<https://doi.org/10.1371/journal.pone.0305255.t001>

Table 2. Independent predictors of obesity prevalence rate.

Variable	β	Std. Error	Sig.
Caloric intake	0.887	0.418	0.036*
GDP	-0.099	0.082	0.227
LMDR	-0.198	0.048	<0.001***
Insufficient.phys.activity	0.242	0.118	0.042*
Antibiotic consumption	-0.009	0.125	0.940

LMDR, Lifetime maternal death rate in 1990; Insufficient.phys.activity, Insufficient physical activity

Based on multiple linear regression modelling using logarithmed variable values. Df1 = 5, df2 = 133. Adjusted R^2 = 0.422.

* $p < 0.05$

*** $p < 0.001$

<https://doi.org/10.1371/journal.pone.0305255.t002>

coefficient of -0.179 (SE = 0.031, R^2 = 0.406 $p < 0.001$) while caloric intake showed a β coefficient of 0.789, (SE = 0.395, R^2 = 0.423, $p < 0.047$ (S2 Table in [S1 Text](#)).

The median lifetime maternal death rate in 1990 was 0.48%. We explored relationships among LMDR, obesity and the confounding variables separately in nations above and below this median. Nations with a LMDR below the median showed a range of LMDR of <0.01% to 0.45%. Nations with a LMDR above the median showed a range of LMDR of 0.48% to 14.93%. Results for countries above the median LMDR, shown in [Tables 3 and 4](#) indicate a stronger association compared to all nations relationship between LMDR and obesity. In nations with LMDR above the median all variables showed a significant association with obesity rates and LMDR ([Table 3](#)) suggesting all other variables are potential confounders. When the four confounding variables are held constant to perform a partial correlation analysis between LMDR and 2016 obesity rates in nations with above the median LMDR a coefficient of $r = -0.573$ ($p < 0.00001$) is obtained (S3 Table in [S1 Text](#)). This association between LMDR and obesity in nations with LMDR above the median when confounders are held constant demonstrates a significantly stronger relationship than the one found across all countries (comparing $r = -0.573$ with $r = -0.336$ yields a significant difference $p = 0.03$, when tested by (<https://www.psychometrica.de/correlation.html>). In multiple regression analysis for this group of countries, with LMDR above the median the LMDR turned out to be the only independent variable significantly influencing obesity rate, with GDP, calorie intake, physical inactivity and antibiotic use showing no independent association with obesity rate in these nations ([Table 4](#), [Fig 2](#) and S3 Table in [S1 Text](#)).

Table 3. Correlation between all variables studied in countries with LMDR above the median.

	Obesity 2016	LMDR 1990	Insufficient physical activity	Caloric intake	GDP	Antibiotic consumption
Obesity 2016	1	-0.705***	0.285*	0.356**	0.428***	0.306**
LMDR 1990	-0.695***	1	-0.373**	-0.457***	-0.620***	-0.468***
Insufficient phys.activity	0.334**	-0.385***	1	0.250*	0.408***	0.165
Caloric intake	0.319**	-0.438***	0.248*	1	0.450***	0.105
GDP	0.449**	-0.647***	0.405**	0.418**	1	0.438***
Antibiotic consumption	0.330**	-0.567***	0.186	0.067	0.540***	1

LMDR, Lifetime maternal death rate in 1990; Insufficient.phys.activity, Insufficient physical activity.

Pearson r (above the diagonal) and nonparametric Spearman's rho (below the diagonal).

Median LMDR = 0.45%.

The table shows bivariate correlations between logarithmed values of all the variables. *** $p < 0.001$; Number of countries: 64–90.

<https://doi.org/10.1371/journal.pone.0305255.t003>

Table 4. Independent predictors of obesity prevalence in countries with LMDR above the median.

Variable	β	Std. Error	Sig.
Caloric intake	0.198	0.564	0.726
GDP	-0.017	0.108	0.872
LMDR	-0.542	0.201	<0.001***
Insuf.phys.activity	0.035	0.144	0.808
Antibiotic consumption	-0.065	0.185	0.726

LMDR, Lifetime maternal death rate in 1990; Insuf.phys.activity, Insufficient physical activity.

Median LMDR = 0.45%.

Based on multiple linear regression modelling using logarithmed variable values. Df1 = 5, df2 = 58. Adjusted R^2 = 0.457. *** $p < 0.001$

<https://doi.org/10.1371/journal.pone.0305255.t004>

In the group of countries with lower than median LMDR, obesity rate did not correlate significantly with LMDR ($r = -0.067$, $\rho = 0.107$, $N = 90$, $p = 0.863$) and it did not show significant contribution to obesity variance in multiple regression analyses. In this group of nations, with LMDR below the median, caloric intake and insufficient physical activity do show significant association with obesity rate (S2 Fig and S4 Table in S1 Text).

Additional analyses were performed only in developing nations to identify the frequency of nations with both high obesity rates and a high Maternal Mortality Rate (MMR). While no clear globally accepted definition of a high obesity nation exists, the definition was obtained using the 2017 obesity update of the Organization for Economic Cooperation and Development (OECD), which reported across the OECD nations 19.5% of the adult population was obese in 2015 [41]. Given a national obesity rate of 19.5% is below the global median rate, it represents a conservative threshold to define a “high obesity nation”, including more than half the nations of the world. Nations with obesity rates higher or lower than 19.5% were referred

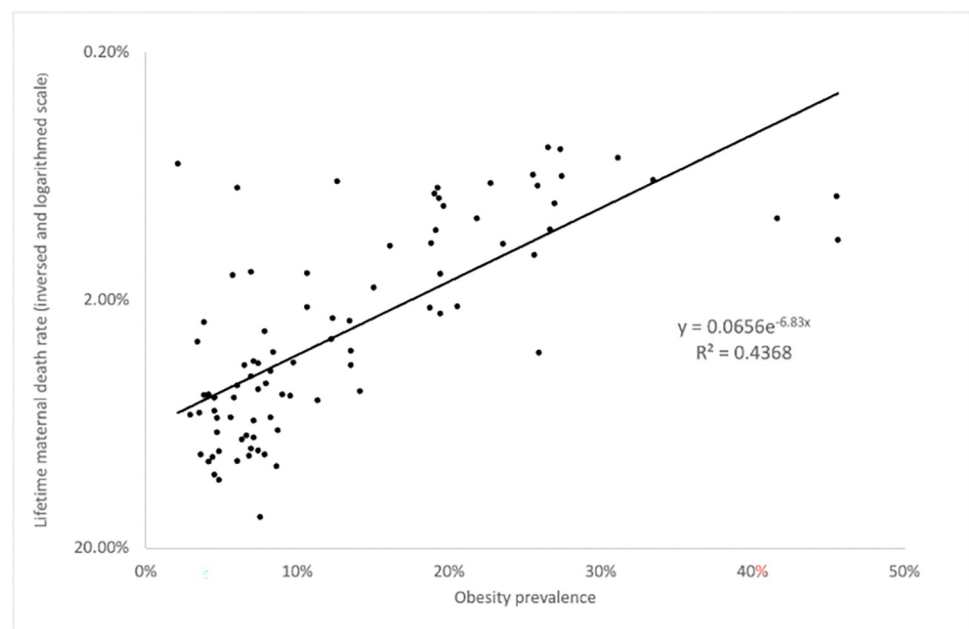


Fig 2. Relationship between obesity prevalence and LMDR in countries with LMDR above the median. LMDR, Lifetime maternal death rate in 1990. Median LMDR = 0.45%.

<https://doi.org/10.1371/journal.pone.0305255.g002>

to as high or low obesity rate nations. High MMR was defined as above 500 deaths in 100,000 live births, given this would include nations with MMRs the World Health Organization classifies as very high or extremely high. Nations with MMRs above or below 500 deaths in 100,000 live births were referred to as high or low MMR nations respectively. Developing nations were defined using those listed as such by the United Nations World Economic Situation and Prospects (WESP).

Given these definitions 128 developing nations were identified with data on obesity rate and MMR. Of these nations 80 were found to have a low MMR and 58 (72.5%) of these low MMR nations had high obesity rates. Among 48 developing nations with high MMR, only one nation had a high obesity rate (2%). The difference in high obesity rates between nations with low MMR (72.5%) and high MMR (2%) is large and significant (Chi Squared = 42.592 $P < 0.00001$). To ensure these results were not entirely driven by the more developed nations, the same analysis was performed in only the least developed nations, and only in low-income nations as defined by WESP. All analyses identified multiple nations with low MMR to have high obesity rates, and only one nation with high MMR had high obesity rates all showing significant differences, details of these additional analyses can be found in the [S1 Text](#).

Discussion

The results of our three analyses come together to offer support of the microevolutionary hypothesis. Our primary analysis identified 1990 LMDR to be strongly associated with modern obesity rates. With confounding variables held constant, 1990 LMDR was demonstrated to be independently associated with national obesity rates explaining 11% of the variance between nations, while the other variables examined: GDP, calorie intake, physical inactivity, and antibiotic use, were all correlated with obesity variance, LMDR was the most strongly correlated, with the largest effect size. Similar to LMDR, historical neonatal mortality was associated with modern obesity, however the association was not as strong as LMDR. This would be predicted by the micro-evolutionary hypothesis given LMDR includes two strong factors influencing selection pressure—maternal mortality and fertility rate, while neonatal mortality only contains a single factor. In addition, maternal mortality by itself would likely represent a stronger selection pressure than neonatal mortality given that neonatal mortality has a number of factors, many not related to a neonate carrying obesity genes.

Our second analysis further supported the microevolutionary hypothesis. In this analysis the nations were divided in half with the median LMDRs (0.48%) serving as the dividing line, examining nations above and below the median separately. In nations with LMDR below the median no independent association of LMDR with obesity rate was found after controlling for the other variable. This finding was what the microevolutionary hypothesis would predict, given the median LMDR was 0.48%, and therefore when comparing nations below the median, the differences in LMDR are a fraction of a percent and therefore would produce negligible differences in negative selection pressure to be able to identify differences in obesity rates over such a short time scale. However when comparing nations with LMDR above the median the difference ranged from 0.48% to 14.93%, which creates large variation in negative selection pressure. As predicted in nations with high LMDR, when confounding variables were controlled for, lifetime maternal death rate explains 33% of the variance in obesity rates between nations.

In addition this analysis found calorie intake and physical inactivity to be correlated with obesity in nations with LMDR below the median, as would be expected. However, in nations with above median LMDR, calorie intake and physical inactivity showed no association with obesity rate. This surprising finding that calorie intake and physical inactivity have no

association with obesity rates in half of nations with LMDR above the median calls into question if these two factors can be major drivers of the global obesity epidemic. Simultaneously it is logical why many obesity researchers concluded that the obesity epidemic's major drivers are increased calorie intake and physical inactivity, given most studies on obesity have been conducted only in developed nations with low LMDR, and in these nations calorie intake and physical inactivity are associated with obesity [45, 46]. Yet given all nations have experienced an increasing obesity rate since 1990, we suggest that it is simply not possible for calorie intake and physical inactivity to be major drivers of the obesity epidemic if they show no association with obesity rate in half of the nations of the world. Interestingly, calorie intake and physical inactivity both have a similar range of values in nations above and below median LMDR, with average calorie intake ranging from approximately 2,000 to 3,500 in both. Physical inactivity also showed a similar range in nations with above and below median LMDR ranging from approximately 10% to 55% in both. The major driver of the obesity epidemic must explain without exception the global nature of the phenomenon. While increased calorie intake and physical inactivity have likely contributed to worsening obesity in many nations, these factors and others which have been proposed do not explain rising obesity in all nations, given in many the expected directional association is not observed. Obstetrical outcomes have improved in every nation globally without exception (Ourworldindata.org), the microevolutionary hypothesis offers a parsimonious explanation for a single cause that has led to increasing obesity rates in all nations, but does not challenge these other proposed factors also play some role.

The third analysis performed only in developing nations found that those with low 1990 MMR, 72.5% have high modern obesity rates, but only one nation (2%), Haiti possessed a high MMR and high obesity rate. It should be noted that in the third analysis MMR was used in place of LMDR. While LMDR is a superior variable for evaluating potential selection pressure changes given it also includes fertility, MMR was used in this analysis given the WHO offers a widely accepted definition for high MMR, but does not do so for LMDR. The definitions used to identify nations with high obesity and high maternal mortality were based on the WHO definition (>500 in 100,000 live births) and average obesity rates of OECD nations (19.5%), and were relatively arbitrary thresholds in their relationship to evolutionary pressures. Haiti's MMR and obesity rate were both near these arbitrarily thresholds with a MMR of 625 in 100,000 live births and obesity rate of 22.7%. Interestingly the only other high MMR nations with obesity rates within 5% of our chosen threshold all had MMR rates near the MMR threshold as well suggesting evolutionary pressure is reduced at a higher MMR rate than the threshold chosen for the analysis.

Study limitations

The limitations of this study's findings are that all analyses demonstrated statistical associations, of which causation can not be assumed given potential unforeseen confounders. It is possible some other medical interventions are the cause of the obesity epidemic and they may increase in use within a population at a similar temporal pattern as obstetrics lowered LMDR. Antibiotic prescriptions were evaluated as a surrogate for other medical interventions limiting mortality. They demonstrated a much weaker correlation with obesity than LMDR, thus making the general drop in mortality less likely specific cause of increased obesity. Our study did examine calorie intake and physical inactivity. These variables had a weaker correlation with obesity than LMDR but were significant contributors. A limitation is that it remains plausible that other environmental effects we did not test for could be confounded with LMDR and better explain the association. It is obvious that increase in human body mass is a multivariate phenomenon, and many factors may influence it to some degree. We do not deny some factors

other than LMDR have influenced the rise in obesity in some nations, just state that the LMDR as a factor of natural selection had the main impact on the rise of obesity experienced by all nations.

Further limitations include the limited data for national LMDR prior to 1990, and obesity rates prior to 1975 preventing closer examination of how earlier differences in LMDR may have influenced obesity rates in different nations at earlier time points.

In addition, alternative hypotheses to a rapid gene pool change suggested by the microevolutionary hypothesis may explain the strong associations between LMDR and obesity identified in this study. One such potential alternative hypothesis could be that heritability of obesity is explained by telomere length heritability rather than gene heritability. A second alternative hypothesis that could explain the LMDR and obesity association is that maternal obesity influences long-term offspring obesity risk via in-utero maternal effects likely via altered hormone signals between obese mother and fetus.

Social implications

The hypotheses suggesting environmental changes in diet and physical activity as the major causes of the obesity epidemic, imply those with obesity must lack “willpower” to eat healthy and exercise. This wide-held belief has resulted in great social stigma for those suffering from obesity, indirectly blaming obese individuals for the cause of their state. While dieting and exercise can occasionally reduce body weight and thus BMI, nearly all long-term studies find dieting and exercise do not lead to sustained weight loss in the large majority of obese individuals. The microevolutionary hypothesis may alleviate some of the social stigma of obesity, by clarifying that the cause of most individuals’ obesity is the result of a collection of genes they were born with. Blame is not typically placed on those with genetic conditions that cause a pathological state. The microevolutionary hypothesis would hopefully help the general and medical communities understand that the cause of most individuals’ obesity is second to a genetic cause, and to stop stigmatizing obese individuals for the false belief that their lack of willpower is the cause of their obesity. With decreased stigma of obesity, it is plausible both physicians and patients would be more open to treating obesity with effective medical interventions such as bariatric surgery and/or medications.

Supporting information

S1 Text. Supporting information file includes S1, S2 Figs, S1-S4 Tables and S1, S2 Files. (DOCX)

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