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Journal

Pediatric Obesity, 13(5)

ISSN

2047-6302

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Publication Date

2018-05-01

DOI

10.1111/ijpo.12210

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Obes. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Pediatr Obes. 2018 May ; 13(5): 312–320. doi:10.1111/ijpo.12210.

Air pollution, weight loss and metabolic benefits of bariatric surgery: A potential model for study of metabolic effects of environmental exposures

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Abstract

Background—Emerging experimental evidence suggests air pollution may contribute to development of obesity and diabetes, but studies of children are limited.

Objectives—We hypothesized pollution effects would be magnified after bariatric surgery for treatment of obesity, reducing benefits of surgery.

Methods—In 75 obese adolescents, excess weight loss (EWL), high denslty lipoprotein (HDL) cholesterol, triglycerides, alkaline phosphatase (ALP), and hemoglobin A1c (HbA_{1c}) were measured prospectively at baseline and following laparoscopic adjustable gastric banding (LAGB). Residential distances to major-roads and the average two-year follow-up exposure to particulate matter <2.5 micrometers ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone were estimated. Associations of exposure with change in outcome and with attained outcome two years post-surgery were examined.

Results—Major-roadway proximity was associated with reduced EWL and less improvement in lipid profile and ALP after surgery. NO_2 was associated with less improvement in HbA_{1c} and lower attained HDL levels and change in triglycerides over two years post-surgery. $PM_{2.5}$ was associated with reduced EWL and reduced beneficial change or attained levels for all outcomes except HbA_{1c}.

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Conflicts of Interest Disclosures

Conflict of interest: Fred Lurmann and Rob McConnell have received support from an air quality violations settlement agreement between the South Coast Air Quality Management District, a California state regulatory agency, and BP. The other authors have no potential conflicts of interest to declare.

Conclusions—Near-roadway, $PM_{2.5}$ and NO_2 exposures at levels common in developed countries were associated with reduced EWL and metabolic benefits of LAGB. This novel approach provides a model for investigating metabolic effects of other exposures.

Keywords

Air pollution; obesity; metabolic syndrome; lipids; bariatric surgery

INTRODUCTION

Over the last several decades the worldwide prevalence of obesity and type 2 diabetes has increased markedly, especially in developed Western countries (1, 2). Increased caloric intake and reduced physical activity are likely causes of the epidemic (2). However, emerging evidence indicates that prenatal and childhood environmental exposures, including nicotine, anthropomorphic combustion products, and environmental endocrine disrupting chemicals, may also contribute to the development of obesity and its metabolic consequences (3–5).

Recent animal toxicological and human epidemiological studies suggest that particulate and near-roadway air pollution (NRAP) may cause obesity and exacerbate metabolic abnormalities, including insulin resistance, dyslipidemia and type 2 diabetes (5, 6). In experimental mouse models, early life exposure to aerosolized urban particulate matter less than 2.5μm in aerodynamic diameter ($PM_{2.5}$) resulted in fatty liver, liver injury and altered balance of lipolysis and lipogenesis (5). PM-induced increased visceral adipose tissue led to insulin resistance and abnormal glucose homeostasis. Epidemiological studies found associations of markers of residential NRAP with increased trajectory of body mass index (BMI) or obesity in children (6). A meta-analysis of epidemiological studies found associations of residential $PM_{2.5}$ and nitrogen dioxide (NO_2) exposure with type 2 diabetes (7). Exposure to NO_2 and particulate matter have also been associated with insulin resistance in children (8).

Bariatric surgical intervention causes rapid weight loss in obese patients and improves insulin resistance and indicators of cardio-metabolic health, including hemoglobin A_{1c} (HbA_{1c}), serum lipids and non-alcoholic fatty liver disease (9, 10). Using bariatric surgical patients as a model to investigate effects of environmental exposure, one recent study found that improvement in triglyceride concentration and markers for liver injury were reduced in subjects with high concentrations of endocrine disrupting chemicals in adipose tissue (11). We hypothesized that the large and rapid metabolic changes after bariatric surgery might also magnify effects of air pollution and that the benefits of surgical intervention would be reduced by exposure. Because the metabolic improvement after bariatric surgery is larger in patients with shorter duration of metabolic disease (10), we examined this hypothesis in a population of morbidly obese adolescents undergoing laparoscopic adjustable gastric banding (LAGB).

METHODS

Study participants

Ninety-eight obese adolescents undergoing LAGB were enrolled between May 2005 and November 2013, and follow-up through February 2014 was included in this analysis. The majority of participants lived in or near New York City (Supplemental Figure S1). After exclusion of subjects missing residential address or who did not have complete information on residential exposure to all three regional pollutants [$PM_{2.5}$, NO_2 and ozone (O_3)], there were 75 participants included in analyses. (See Online Supplemental material for details).

Written informed consent was obtained from parents or legal guardians and assent was obtained from participants. Analyses were approved by both the New York University and University of Southern California institutional review boards (IRBs).

Outcomes

Outcomes included excess weight loss (EWL), HbA_{1c}, a time-integrated index of hyperglycemia, serum levels of alkaline phosphatase (ALP), a marker for liver injury, and triglycerides and high-density lipoprotein (HDL) cholesterol. EWL was calculated as follows:

$$EWL = \frac{Weight\ before\ surgery - follow\ up\ weight}{Weight\ before\ surgery - ideal\ body\ weight} \times 100$$

where follow-up weight was measured during each follow-up visit after surgery, and ideal body weight was the weight-for-height corresponding to BMI of 25kg/m^2. Weight was measured by a trained technician on a calibrated scale after the participant removed shoes and emptied pockets. Data were collected prior to or at the time of admission for surgery (baseline). Thereafter, weight and height were collected at 2 and 6 weeks, 3, 6, 9 and 12 months in the first year and every 12 months thereafter. Laboratory measurements were made at baseline, 3, 6, 9 and 12 months, and every 12 months thereafter.

Air pollution exposure assignment

Details of the exposure assignment are provided in the Supplemental Material. Briefly, participants' residential addresses were geocoded using ArcMaps 10.2. Distance to the nearest major road was estimated using ESRI's ArcGIS tools (Version 10.3, ESRI, Redlands, CA, www.esri.com). Minimum residential distances of each participant to the nearest major road (FCC1-limited access highways, FCC2-unlimited access roads or FCC3-secondary and connecting roads, as defined by the U.S. Department of Transportation) were computed. Ambient air quality data from the U.S. Environmental Protection Agency's Air Quality System were acquired for 2005–2014. Monthly average daily $PM_{2.5}$, NO_2 and O_3 values from up to four air quality monitoring stations within 50km were spatially interpolated to participant residences using inverse distance-squared weighting. Monthly averages were aggregated to obtain average exposure during the two years following each participant's surgery.

The 2-year average regional pollutant exposures were categorized based on the tertile distribution of each pollutant and were also examined as continuous exposures. The tertile cut-points were 10.1 and 11.3 μg/m^3 for $PM_{2.5}$, 18.5 and 20.7 ppb for NO_2 and 23.3 and 26.7 ppb for O_3. Proximity to a major road was highly skewed, mean 282m but extending to 1421m. Proximity was dichotomized into those living >100m and those living ≤100 m, based on prior studies showing large spatial gradients and markedly larger exposure to near-roadway pollutants within 100m compared with distances further away (13) and on sufficient study population.

Covariates

Information was available on participants' age, gender and race/ethnicity. Each participant was asked at study enrollment and at each follow-up visit if he/she exercised, how many times per week, and the type of exercise performed (e.g. running). At each follow-up visit, participants were asked if the amount of food consumed was the same, one-half, one-quarter, or less than one-quarter the amount of food consumed prior to surgery. A questionnaire assessed the monthly frequency of fast food consumption. Information on family socioeconomic status was not collected. Therefore, we assigned 2007–2011 Census group block estimates of percent of families living below the poverty level, percent of adults unemployed, household median income, median home value, and percent minority corresponding to the residence of each child.

Statistical analysis

To account for non-linear trends over time and for multiple measurements per subject, for each outcome we fit a piecewise linear spline model nested within a hierarchical mixed-effects modeling structure (14). A product term of pollutant with time since surgery estimated the association of change in each outcome with pollution. The model allowed for separate curves for different exposure categories and also included adjustments for time varying and time invariant covariates at the time of surgery.

We report the effect of each pollutant on both the 2-year post-surgery change and on the attained value of the outcome 2 years after surgery. We examined associations of each outcome with exposure to $PM_{2.5}$, NO_2 and O_3. The exposure-response relationships for some models were non-linear, but nonlinearity was not consistent across pollutants and outcomes. Therefore, for simplicity and interpretability of results, the primary analysis was based on tertile-specific effects of regional exposures. We assessed a linear trend coded as 0, 1 or 2 across tertile-specific estimates of regional pollutant exposure. A p-value less than 0.05 was considered statistically significant assuming a two-sided hypothesis test. Analysis was conducted in STATA 13.1 (15). (See Online Supplemental material for additional details of the analysis).

RESULTS

Twenty-one (28%) of participants were female. Participants were predominantly Non-Hispanic White (71%); 15% were Hispanic; 13% were Black, and 1.0% other (Table 1). Almost one-third of the participants resided within 100m of a major road. Mean of the 2-

year (post-surgery) average $PM_{2.5}$ exposure was 11μg/m^3 (standard deviation (SD) 1.7); mean NO_2 was 19ppb (SD 5.6) and mean O_3 25ppb (SD 3.1).

Mean pre-surgical BMI was 48kg/m^2 (SD=7.1; Table 2). Mean HDL was 42mg/dL (SD 9.1); mean triglyceride was 119mg/dL (SD 59); mean ALP was 109U/L (SD 44); and mean HbA_{1c} was 5.6% (SD 0.32).

In order to illustrate the pattern of change in the outcomes over time, we plotted raw (unadjusted) measurements as a function of time since surgery. There were non-linear changes over time for all five outcomes (Figure 1). For EWL, for example, a large decrease in weight (increase in EWL) occurred during the first year and leveled off during the second year following surgery. As illustrative of the impact of pollution, the pattern of EWL is plotted by residential proximity greater than 100m (triangle) and within 100m of a major road (circle) in Figure 2. The reduction in change in EWL during 2 years and lower attained EWL 2 years after surgery, estimated from the modeled effect of proximity (adjusted for sex, age, race/ethnicity and weight at the time of surgery), is shown for participants living closer to a major road.

The modeled estimates of the change in EWL during two years after surgery was 43% (95% CI: 39, 46) among those living further than 100m of a major road, compared to 34% (95% CI: 29, 39) among those who lived within 100m (p=0.005; Table 3). Attained EWL 2 years after surgery was 47% and 40%, respectively (p=0.02). There was reduced change in EWL with increasing $PM_{2.5}$ tertiles (48% in tertile 1, 40% in tertile 2 and 38% in tertile 3; p trend=0.007). Attained EWL was 52% in $PM_{2.5}$ tertile 1, 44% in tertile 2 and 45% in tertile 3 (p trend=0.04). Change in HDL also varied by roadway proximity, 10mg/dL in those living away from a major road compared to 7.0mg/dL in the group living within 100m (p=0.04). The increase in attained HDL after surgery was less with increasing $PM_{2.5}$ tertile of exposure, 54, 51 and 48mg/dL, respectively (p trend=0.02). Attained HDL was also inversely associated with NO_2 tertiles (p=0.01). The reduction (change) in triglyceride levels was greater in those further from a major road, 43 compared to 27mg/dL for those within 100m (p=0.03). Smaller reduction in triglyceride levels was observed across increasing tertiles of $PM_{2.5}$ (50, 35 and 30mg/dL, respectively; p trend=0.02) and NO_2 (55, 33 and 27mg/dL; p trend=0.003). However, the reduction in triglycerides increased with increasing O_3 tertiles (25, 40 and 53mg/dL; p=0.004). The reduction in ALP levels was 34U/L in those living further from a major road compared to 25U/L within 100m (p=0.04). The reduction was also less across increasing $PM_{2.5}$ tertiles (37, 34 and 24U/L; p=0.01). HbA_{1c} decreased less with increasing tertiles of NO_2 exposure (0.27%, 0.23% and 0.15%, respectively; p=0.04).

In sensitivity analyses we adjusted these results for participants' reports of the amount of food consumed at each follow-up visit, frequency of fast food consumption, exercise and for each of the contextual covariates based on Census block of each child's residence, included one at a time in the model to assess potential confounding of pollutant effects. The pattern of estimated pollutant effects on each outcome was quite similar after adjustment and remained statistically significant, with the exception of the association of $PM_{2.5}$ with attained excess weight loss 2 years after surgery. This effect estimate was modestly confounded and the

trend across tertiles was no longer significant after adjustment for Census block percent living in poverty (p=0.09), median home income (p=0.15), and median home value (p=0.07). However, the slope of 0–2 year change in excess weight loss associated with $PM_{2.5}$ remained significant after adjustment for Census block covariates. In addition, in analyses of associations in Table 3 restricted to residences within 25 Km of the nearest monitor, we saw similar or larger effects and all statistically significant trends remained significant.

DISCUSSION

Major roadway residential proximity, a proxy marker of NRAP exposure, was associated with reduced EWL and reduced improvement in lipid profile and ALP during two years after LAGB in morbidly obese adolescents. NO_2, which is both a marker for the NRAP mixture and a regional pollutant reflecting anthropogenic combustion sources (16), was associated with less improvement in HbA_{1c} and with reduced benefit in the attained levels of HDL and change in triglycerides during two years after surgery. Exposure to $PM_{2.5}$, a regional pollutant with relatively homogeneous intra-urban concentrations, was associated with reduced weight loss and reduced beneficial change or attained levels for all outcomes except HbA_{1c}. These results suggest that detrimental associations of near-roadway and regional combustion source pollution with obesity and associated metabolic abnormalities observed in epidemiological studies (5–7) may have been magnified in this study by the massive weight loss and metabolic changes induced by bariatric surgery. These associations with reduced weight loss and with reduced metabolic benefits after bariatric surgery occurred at exposures common across the United States and other developed countries. For example, the 75^{th} percentile of the 2-year average $PM_{2.5}$ distribution (11.9μg/m^3) was lower than the U.S. yearly standard of 12 μg/m^3.

The magnitude of estimated air pollution effects was large. For example, residential proximity to a busy road was associated with approximately one-third, one-quarter and one-fifth of the benefit of surgery for HDL, ALP and EWL, respectively (Table 3); and NO_2 effect estimates across tertiles were associated with almost half the surgically produced reduction in HbA_{1c} and over half the reduction in triglycerides. The 9% difference in two-year loss of excess weight associated with proximity to a busy road would be equivalent to 4kg less weight lost for a person with enrollment height 1.68m (the sample mean) and BMI 40kg/m^2. Although only qualitatively comparable, this difference is almost as large as weight loss that might be expected from a comprehensive behavioral intervention in children, reported to result in a one-year 1.9–3.3kg/m^2 change in BMI, equivalent to weight loss of 5.4–9.3kg, and substantially larger than 2.4kg loss achieved with treatment with orlistat in a person 1.68m tall with BMI 40 (17). The 5mg/dL difference in the increase in attained serum HDL level across $PM_{2.5}$ tertiles is more than twice the average reduction of 2mg/dL that might be expected to result from treatment with fibrates (18).

Animal models provide insight into plausible biological pathways that may explain the association of air pollution with reduced weight loss and impaired metabolic benefits (5, 6). Diesel exhaust particulate, a model near-roadway pollutant, and regional urban PM might influence energy balance and weight through pro-inflammatory effects on the brain affecting appetite or anxiety-associated overeating, mitochondrial damage and resultant skewing of

metabolic balance from energy utilization to storage, endocrine disrupting effects (for example expression of PPARγ), or reduced catecholamine-induced lipolysis (6). Complementary studies of metabolic outcomes have demonstrated immune activation in mice exposed early in life to aerosolized $PM_{2.5}$, resulting in systemic and tissue-specific oxidative stress and pro-inflammatory responses in adipose tissue, liver, and brain, effects which may be synergistic with those of a high-fat diet (5). Visceral adipose tissue volume and a pro-inflammatory immune profile with a skewing of adipose tissue immune response from a Th2 to Th1 type caused by $PM_{2.5}$ exposure resulted in insulin resistance and abnormal glucose homeostasis. $PM_{2.5}$ exposed mice also had increased triglyceride levels, more lipogenesis, and fatty acid uptake and reduced liver glycolysis (19). In humans, elevated levels of total cholesterol and HbA_{1c} were also associated with $PM_{2.5}$ and NO_2 exposures (8, 20). These studies are consistent with emerging evidence from human epidemiological studies showing associations of NRAP and regional $PM_{2.5}$ and NO_2 with obesity and type 2 diabetes (6, 7).

There are few epidemiological studies examining associations of air pollution with liver injury. However, the mobilization of lipophilic persistent organic pollutant polychlorinated biphenyls and dioxins from fat during weight loss after bariatric surgery was associated with markers of liver toxicity and lipid abnormalities (11). In an obese mouse model the benefits of induced weight loss on glucose homeostasis were not observed in animals fed a diet high in polychlorinated biphenyls (21). These studies suggest that the massive weight loss induced by bariatric surgery is a useful model for examining effects of environmental exposure, including air pollution.

High levels of serum ALP can be due to liver dysfunction in obese individuals (22). ALP is also a marker of bone turnover, and significant decrease in bone mineral density due to malabsorption with subsequent increase in ALP has been reported after Roux-en-Y gastric bypass (23). Reduction in bone mineral density has also been associated with NRAP exposure and might be expected to increase ALP (24). Unlike Roux-en-Y gastric bypass, weight loss after LAGB occurs as a result of increased satiety and is thought not to result in malabsorption (22). Our results showing decreasing ALP levels after LAGB are consistent with a liver source, with smaller improvement in patients living closer to major roads or with high $PM_{2.5}$ exposure.

There were some limitations to this study. O_3 exposure was associated with improving triglycerides during the two years after surgery. Exposure misclassification and an inverse correlation between O_3 and other regional pollutants (Spearman's $\rho=-0.5$ for $PM_{2.5}$ and $\rho=-0.6$ for NO_2) could play a role in these anomalous results. Further investigation is warranted. Of those enrolled in the study from which the outcome data were obtained, 23 subjects (23%) were excluded because they did not have complete exposure information. The demographic characteristics of those excluded due to missing pollution data and those included in the analysis were generally similar except for race/ethnicity, with a greater proportion excluded among non-Hispanic Whites (Table 1 in the Online Supplement). Although it is possible that these exclusions introduced bias that could have explained the observed results, in sensitivity analyses unadjusted for ethnicity the pattern of associations was almost identical to that in the Table 3 adjusted results, suggesting that ethnicity itself

was not likely to be responsible for selection bias. One-third of the sample was lost to attrition during the first two years of follow-up. However, restricting the analysis to those with at least two years of follow-up did not change the results substantially. The pattern of associations of air pollution with metabolic outcomes was not confounded by dietary and exercise information available for this analysis. Results were generally robust to adjustment for Census block contextual characteristics suggestive of low socioeconomic status. We cannot rule out residual confounding that might have been identified if additional indicators of behavioral (eg. smoking) and family socioeconomic confounders were available. Noise was not measured, but has been found in other studies both to be correlated with ambient exposure to oxides of nitrogen and to be associated with diabetes, independent of effects of air pollution (25), and with higher BMI in adults (26).

We also considered the possibility that improvements in surgical techniques or other factors that changed over the course of the study could result in improved outcomes and, if correlated with temporal trends in exposure, might confound the effect of pollution. $PM_{2.5}$ has substantially decreased across the United States, including New York City, during the period of this study, so much so that the year of enrollment variable was fairly highly correlated with $PM_{2.5}$ ($R=-0.8$). Therefore, it is was not possible to adjust the effect of $PM_{2.5}$ for the effect of year of enrollment. However, a continuous variable for integer year of entry into the study was associated only with the 2-year slope of triglycerides (−2.9 mg/deciliter for each year of the study), so it is unlikely that the broad pattern of associations was explained by temporal improvements in the effect of surgery.

High energy intake and low levels of physical activity are important causes of the epidemic of childhood obesity and type 2 diabetes, but the results of this study support the growing body of evidence that exposure to air pollution and other environmental exposures may also contribute to the development of these outcomes. Our results suggest that air pollution may attenuate the benefits of bariatric surgery. Additional research is needed to determine whether these results can be replicated, to investigate the potential mechanisms underlying these novel findings, and to examine the impact of air pollution on the success of other obesity and obesity-related disease interventions. Variability in the trajectory of weight loss and improvement in metabolic outcomes after bariatric surgery may also provide a novel model for investigating metabolic effects of other environmental exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding was provided by the National Institutes of Health (grants #P01ES022845, R21ES024707 and P01ES009581), and the U.S. Environmental Protection Agency (grant #RD083544101). Support was also provided by funds from an air quality violations settlement agreement between the South Coast Air Quality Management District, a California state regulatory agency, and BP.

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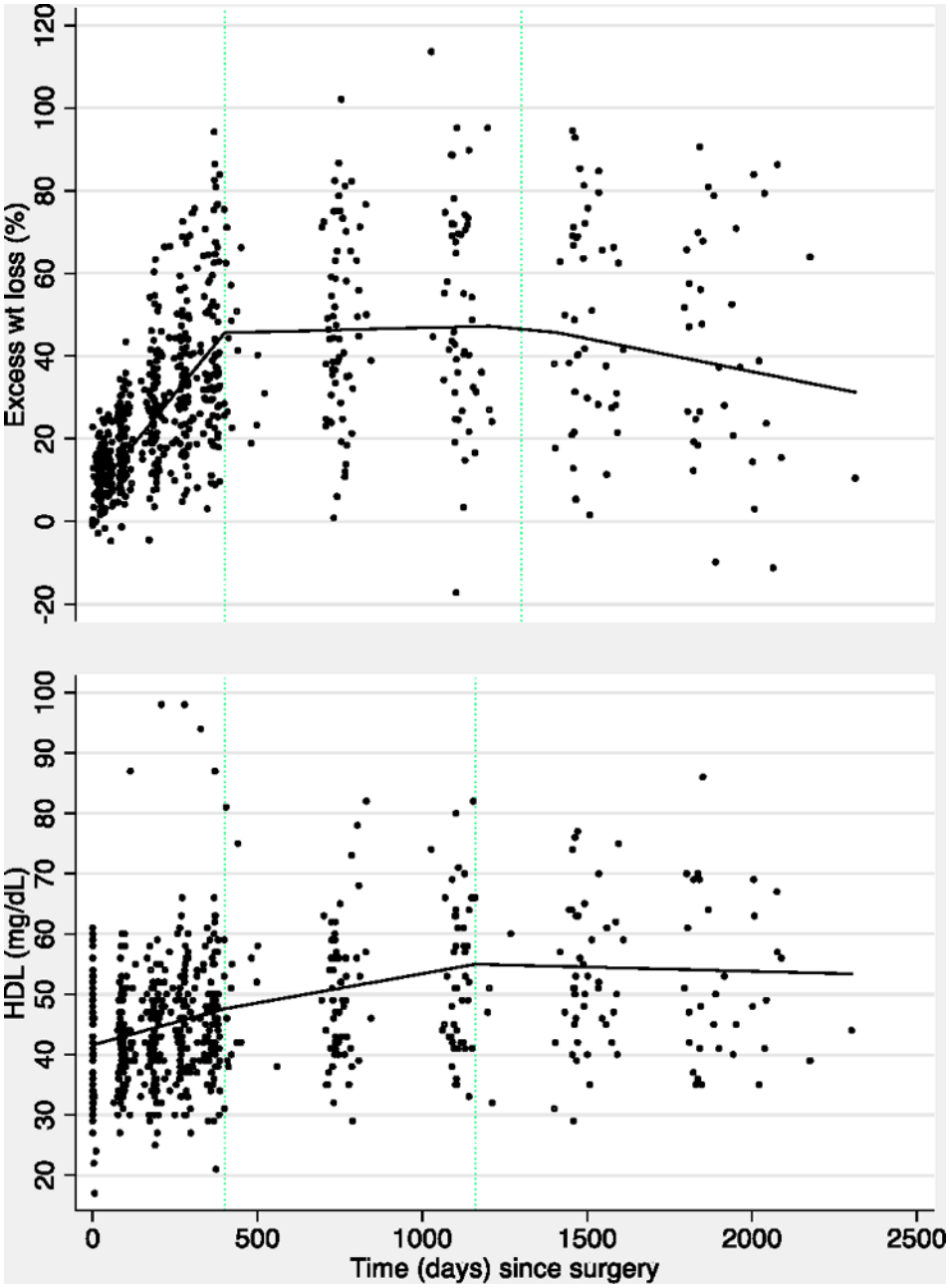
What is already known on the subject

1. Bariatric surgery results in weight loss and improvement in metabolic outcomes in morbidly obese patients.

What this study adds

1. Exposure to near-roadway and regional air pollution was associated with reduced weight loss and improvement of metabolic outcomes after bariatric surgery. Obese patients undergoing bariatric surgery may provide a novel model for investigating metabolic effects of environmental exposures.



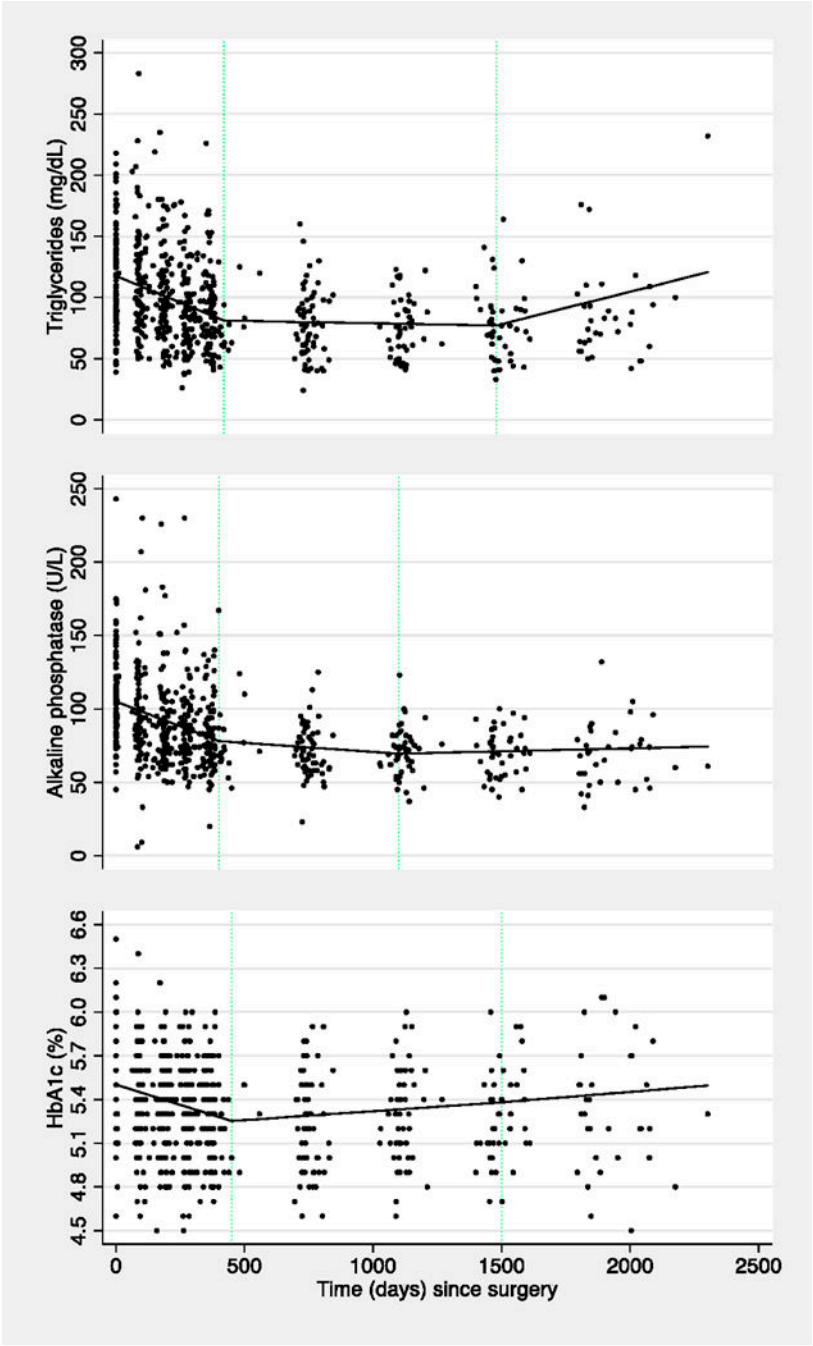


Figure 1.

Non-linear temporal trends of excess weight loss, high-density lipoprotein (HDL), triglycerides, alkaline phosphatase and hemoglobin A_{1c} (HbA_{1c}) after surgery.

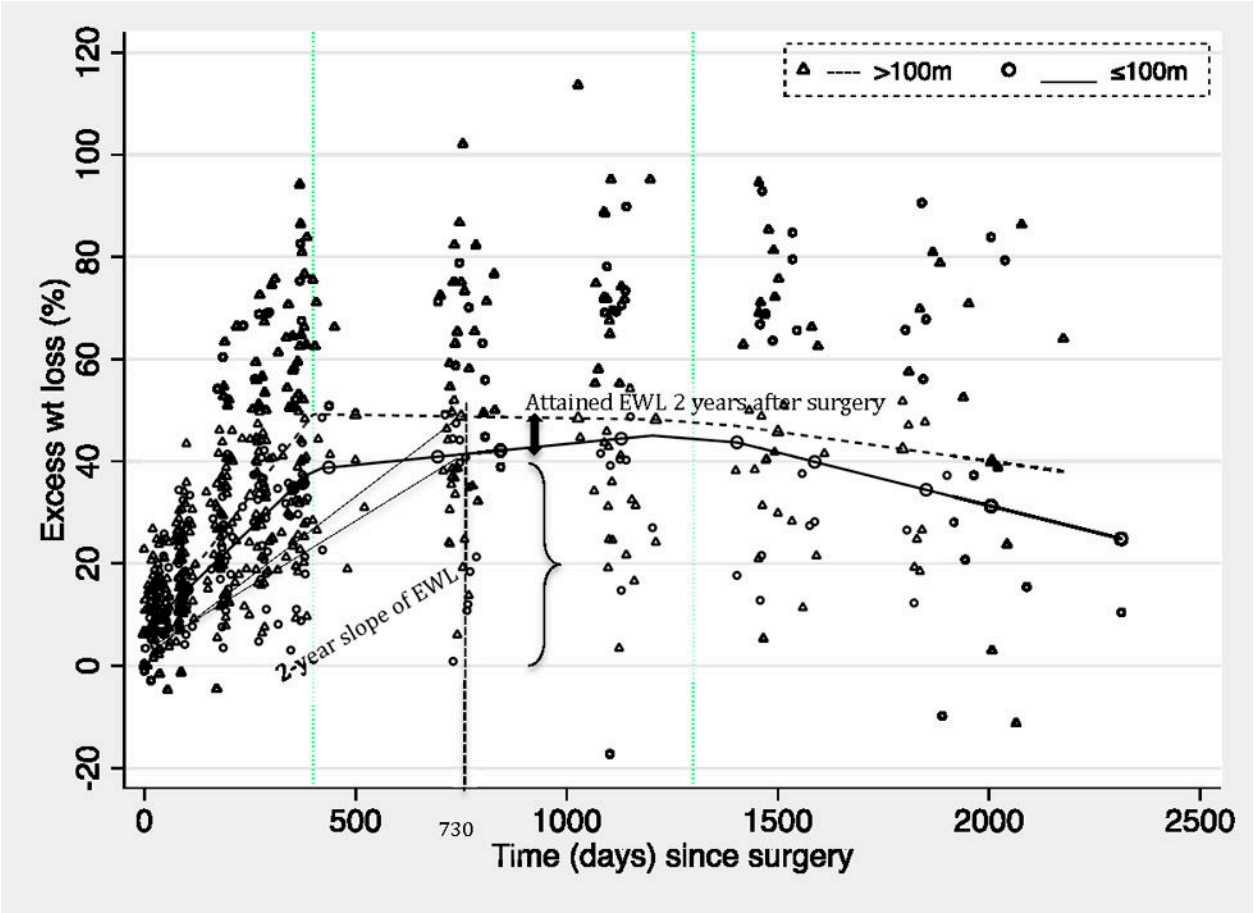


Figure 2.

Excess weight loss (EWL) after surgery, by category of distance to a major road [greater than 100m (triangle, dashed smooth), less than 100m (circle, solid smooth)], with the adjusted 2-year slope and attained EWL from the analytical model superimposed.

Table 1

Characteristics of the study participants and distribution of near-roadway and regional air pollution.

	N (%)	
Race/ethnicity		
White	53 (70.7)	–
Black	10 (13.3)	–
Hispanic	11 (14.7)	–
Other	1 (1.3)	–
Residential proximity <100m to a major road	24 (32.0)	
2-year average $PM_{2.5}$ ($\mu g/m^3$), Mean (SD*)	–	10.7 (1.69)
Median (IQR*)		10.7 (9.38 – 11.9)
Min - Max	–	7.27 – 14.4
2-year average NO_2 (ppb), Mean (SD*)	–	19.3 (5.56)
Median (IQR*)		19.3 (17.6 – 23.3)
Min - Max	–	4.25 – 34.3
2-year average Ozone (ppb), Mean (SD*)	–	24.9 (3.14)
Median (IQR*)		24.7 (22.5 – 27.0)
Min - Max	–	17.7 – 31.1

*SD: Standard deviation, IQR: Interquartile range

Table 2

Baseline distribution of body mass index (BMI), lipids, alkaline phosphatase and hemoglobin A_{1c} (HbA_{1c}) in study participants.

	Mean (SD*)	Median (IQR*)	Min - Max
Pre-surgery BMI (kg/m^2)	47.8 (7.1)	45.2 (43.3 – 51.3)	39.6 – 75.8
HDL (mg/dL)	41.5 (9.1)	41.0 (34.0 – 48.0)	17.0 – 61.0
Triglycerides (mg/dL)	119 (58.9)	105 (83 – 146)	39.0 - 469
Alkaline phosphatase (U/L)	109 (44.2)	100 (83.0 – 120)	45.0 – 319
HbA_{1c} (%)	5.56 (0.32)	5.60 (5.30 – 5.80)	4.80 – 6.50

*SD: Standard deviation, IQR: Interquartile range

Table 3

Association (regression coefficients, 95% CI[*]) of near-roadway air pollution[†] and regional air pollution ($PM_{2.5}$, NO_2 and O_3) with excess weight loss (EWL),[‡] HDL, triglycerides, alkaline phosphatase (ALP) and hemoglobin A_{1c} (HbA_{1c}) during 2 years after bariatric surgery.

	EWL (%)		**HDL (mg/dL)**		**Triglycerides (mg/dL)**		**ALP (U/L)**		**HbA_{1c} (%)**	
	0–2 year change	**Attained at 2 years**	**0–2 year change**	**Attained at 2 years**	**0–2 year change**	**Attained at 2 years**	**0–2 year change**	**Attained at 2 years**	**0–2 year change**	**Attained at 2 years**
Proximity to major roads										
>100m	42.6 (39.2, 46.0)	47.0 (43.0, 51.0)	10.4 (8.41, 12.3)	51.7 (49.0, 54.4)	−43.3 (−52.1, −34.6)	83.5 (73.3, 93.6)	−34.1 (−39.2, −29.0)	64.1 (55.1, 73.1)	−0.24 (−0.30, −0.19)	5.25 (5.16, 5.34)
≤100m	34.1 (29.3, 38.9)	39.9 (34.2, 45.6)	6.97 (4.22, 9.73)	48.9 (45.0, 52.8)	−26.6 (−39.0, −14.3)	97.1 (82.7, 111)	−25.0 (−32.1, −17.9)	69.5 (56.5, 82.4)	−0.16 (−0.24, −0.09)	5.32 (5.20, 5.45)
P-difference[§]	**0.005**	**0.02**	**0.04**	0.17	**0.03**	0.08	**0.04**	0.43	0.09	0.28
$PM_{2.5}$										
Tertile 1	47.6 (42.2, 53.0)	52.1 (46.2, 58.0)	10.2 (7.22, 13.2)	53.6 (50.0, 57.2)	−50.2 (−63.1, −37.2)	81.6 (67.6, 95.5)	−37.3 (−45.0, −29.6)	61.2 (49.7, 72.7)	−0.21 (−0.29, −0.14)	5.27 (5.16, 5.38)
Tertile 2	39.6 (34.6, 44.5)	44.3 (38.7, 50.0)	9.79 (6.94, 12.6)	50.5 (46.7, 54.3)	−34.6 (−47.6, −21.6)	90.0 (75.5, 104.5)	−33.7 (−41.0, −26.4)	72.9 (60.3, 85.5)	−0.21 (−0.29, −0.13)	5.31 (5.19, 5.44)
Tertile 3	37.8 (33.1, 42.5)	44.7 (39.3, 50.0)	8.56 (5.88, 11.2)	48.4 (44.8, 51.9)	−29.7 (−41.9, −17.6)	87.6 (73.8, 101)	−23.7 (−30.6, −16.8)	63.5 (51.6, 75.4)	−0.24 (−0.32, −0.16)	5.21 (5.09, 5.33)
P-trend[§]	**0.007**	**0.04**	0.42	**0.02**	**0.02**	0.51	**0.01**	0.76	0.64	0.39
NO_2										
Tertile 1	42.5 (37.3, 47.7)	47.3 (41.8, 52.9)	11.5 (8.54, 14.4)	55.1 (51.5, 58.7)	−54.6 (−67.7, −41.5)	81.1 (67.6, 94.5)	−27.1 (−34.7, −19.5)	63.1 (51.5, 74.7)	−0.27 (−0.35, −0.19)	5.31 (5.20, 5.42)
Tertile 2	38.0 (33.5, 42.6)	42.6 (37.3, 47.8)	8.55 (6.01, 11.1)	49.3 (45.7, 52.8)	−32.6 (−44.0, −21.2)	88.3 (75.0, 102)	−40.4 (−46.9, −33.9)	68.5 (56.8, 80.1)	−0.23 (−0.30, −0.16)	5.20 (5.08, 5.31)
Tertile 3	41.0 (36.0, 46.1)	47.0 (41.6, 52.4)	9.32 (6.52, 12.1)	49.1 (45.5, 52.8)	−26.8 (−39.8, −13.9)	92.3 (78.3, 106)	−22.4 (−29.6, −15.2)	68.8 (56.6, 81.0)	−0.15 (−0.23, −0.07)	5.29 (5.17, 5.41)
P-trend[§]	0.69	0.92	0.30	**0.01**	**0.003**	0.21	0.38	0.45	**0.04**	0.73
O_3										
Tertile 1	33.1 (28.6, 37.6)	40.5 (35.2, 45.9)	7.91 (5.32, 10.5)	48.7 (45.0, 52.5)	−25.2 (−37.0, −13.4)	97.6 (83.9, 111)	−25.6 (−32.3, −18.9)	68.6 (56.0, 81.2)	−0.19 (−0.26, −0.12)	5.17 (5.05, 5.29)
Tertile 2	46.9 (42.5, 51.4)	51.0 (46.0, 56.0)	11.1 (8.54, 13.7)	51.6 (48.3, 55.0)	−39.6 (−51.2, −28.1)	78.8 (66.6, 91.0)	−34.7 (−41.4, −28.0)	68.0 (56.8, 79.1)	−0.22 (−0.29, −0.15)	5.34 (5.24, 5.45)
Tertile 3	40.1 (34.4 45.7)	43.7 (37.7, 50.0)	9.56 (6.29, 12.8)	53.1 (49.1, 57.0)	−52.7 (−67.1, −38.3)	87.3 (72.9, 102)	−30.8 (−39.3, −22.3)	62.4 (49.6, 75.3)	−0.25 (−0.34, −0.16)	5.25 (5.12, 5.37)
P-trend[§]	0.06	0.39	0.44	0.08	**0.004**	0.26	0.35	0.45	0.32	0.32

*From multilevel linear spline model for trend over time with a random intercept adjusted for sex, age, race/ethnicity and weight at the time of surgery.

†Minimum residential distance to any major road dichotomized at 100 m.

‡Excess weight loss (EWL) = (Presurgery weight - weight at follow up) / (Presurgery weight – ideal body weight-for-height).

§P value for the difference (residential distance ≤100m or >100 m from major road) or linear test of trend (across tertiles of regional pollutant).