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Prospective relationships between body weight and physical activity: an observational analysis from the NAVIGATOR study

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To cite: Preiss D, Thomas LE, Wojdyla DM, *et al*. Prospective relationships between body weight and physical activity: an observational analysis from the NAVIGATOR study. *BMJ Open* 2015;**5**: e007901. doi:10.1136/bmjopen-2015-007901

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-007901).

Received 9 February 2015
Revised 7 July 2015
Accepted 23 July 2015

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ABSTRACT

Objectives: While bidirectional relationships exist between body weight and physical activity, direction of causality remains uncertain and previous studies have been limited by self-reported activity or weight and small sample size. We investigated the prospective relationships between weight and physical activity.

Design: Observational analysis of data from the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, a double-blinded randomised clinical trial of nateglinide and valsartan, respectively.

Setting: Multinational study of 9306 participants.

Participants: Participants with biochemically confirmed impaired glucose tolerance had annual measurements of both weight and step count using research grade pedometers, worn for 7 days consecutively. Along with randomisation to valsartan or placebo plus nateglinide or placebo, participants took part in a lifestyle modification programme.

Outcome measures: Longitudinal regression using weight as response value and physical activity as predictor value was conducted, adjusted for baseline covariates. Analysis was then repeated with physical activity as response value and weight as predictor value. Only participants with a response value preceded by at least three annual response values were included.

Results: Adequate data were available for 2811 (30%) of NAVIGATOR participants. Previous weight (χ^2=16.8; p<0.0001), but not change in weight (χ^2=0.1; p=0.71) was inversely associated with subsequent step count, indicating lower subsequent levels of physical activity in heavier individuals. Change in step count (χ^2=5.9; p=0.02) but not previous step count (χ^2=0.9; p=0.34) was inversely associated with subsequent weight. However, in the context of trajectories already established for weight (χ^2 for previous weight measurements 747.3; p<0.0001) and physical activity (χ^2 for previous step count 432.6; p<0.0001), these effects were of limited clinical importance.

Conclusions: While a prospective bidirectional relationship was observed between weight and physical activity, the magnitude of any effect was very small in the context of natural trajectories already established for these variables.

Trial registration number: NCT00097786.

Strengths and limitations of this study

- Bidirectional relationships have been observed between body weight and physical activity in epidemiological studies, but previous studies have been limited by small participant numbers, by measurement of physical activity at only two time points usually many years apart, and by the lack of objective measures of physical activity. We addressed this question in an analysis of 2811 Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial participants who underwent annual objective measures of both weight and physical activity.
- Participants were very well phenotyped at baseline and all had biochemically confirmed impaired glucose tolerance, a condition which carries a very high risk of progression to type 2 diabetes and which therefore represents a clinically relevant group to study.
- This was an observational analysis and therefore not able to provide information on causal relationships and, due to the moderate effect sizes observed, it is possible for unmeasured confounding to explain the weak observed associations.
- Regardless, our results suggest that only a weak prospective relationship of limited clinical importance exists between weight and physical activity when considered in the context of natural trajectories already established for each.

The prevalence of obesity is rising in most countries which reflects a chronic

imbalance between energy intake and energy expenditure.[1] Some studies have suggested that a decline in physical activity has contributed to this trend,[2] while others have suggested that there has been no obvious trend of declining physical activity in recent decades.[3] In cross-sectional analyses, there are clear associations between physical activity level and adiposity, but such analyses do not allow conclusions about the direction of causality to be drawn. This association could potentially be driven by obesity leading to inactivity, inactivity leading to obesity or a combination of both.

Previous studies have explored the associations both between weight and subsequent physical activity, and between physical activity and subsequent weight, to investigate the strength of these relationships. Results have been mixed with the majority of evidence suggesting that baseline weight and increase in weight may be important determinants of subsequent reductions in physical activity (due to the greater difficulty of being active at higher weight), but that activity or change in activity has limited impact on subsequent weight.[4–7] However, such studies have often been limited by small participant numbers, by measurement of physical activity at only two time points, usually many years apart, and by the lack of objective measures of physical activity. This final point is important as inaccurate estimation of physical activity will diminish any apparent effect of physical activity on an outcome measure.[8] As weight is typically measured with greater accuracy and precision than physical activity, studies where physical activity is measured by self-report questionnaire have an inherent bias for the detection of effects of weight or weight change on physical activity levels rather than associations in the opposite direction, due to regression dilution bias effects.

To overcome the limitations of the existing evidence base and provide insight into the direction of causality for the relationship between weight and physical activity at the population level, large-scale longitudinal analyses are required with objective measurement of both physical activity and weight at multiple time points. The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study was a clinical trial conducted in participants with impaired glucose tolerance (IGT). Given its inclusion of a large number of participants with repeated objective measurement of both weight and physical activity, we analysed the NAVIGATOR data set to further investigate the prospective relationships between weight and physical activity.

PARTICIPANTS AND METHODS

NAVIGATOR (ClinicalTrials.gov number, NCT00097786) was a multinational, double-blinded randomised clinical trial with 2×2 factorial design which assessed the ability of nateglinide and valsartan to respectively reduce major cardiovascular events and new-onset diabetes in 9306 participants with IGT. Details of the trial were published previously.[9–11]

Participants

On the basis of general criteria including age and history of cardiovascular disease, possible research participants attended screening clinics to assess their potential recruitment. Individuals with IGT were eligible if they had one or more cardiovascular risk factor and were aged ≥55 years or if they had established cardiovascular disease and were aged ≥50 years. Detailed inclusion and exclusion criteria are provided in previous publications.[9–11] Participants underwent a 75 g oral glucose tolerance test and IGT was defined as a 2 h post-challenge glucose value of 7.8–11.0 mmol/L (with fasting plasma glucose 5.3–6.9 mmol/L). Inclusion of a participant in this analysis required the contribution of a minimum set of data, as detailed below in the Statistical analysis section. All NAVIGATOR participants provided written informed consent.

Lifestyle modification

Participants took part in a lifestyle modification programme, starting at the baseline visit, based on the principles of the Diabetes Prevention Programme[12] and the Finnish Diabetes Prevention Study.[13] This was designed with the aims of achieving and maintaining 5% weight loss, reducing saturated and total fat intake, and increasing levels of physical activity. Physical activity advice was consistent with American Diabetes Association guidance, namely to achieve at least 150 min of moderate intensity activity each week. Participants were not given a specific target for daily step count. Study personnel administered the programme and provided materials to participants at clinic visits within the first year (at 0.5, 1, 3, 6 and 12 months). Subsequent reinforcement of the programme was pursued through telephone contact.

Weight

Body weight was measured to the nearest 0.1 kg in indoor clothing but without shoes at each visit (conducted at 0.5, 1, 3 and 6 months, then every 6 months) using the same scale. Annual weight data were used for this analysis.

Step count

Ambulatory activity was measured objectively with research grade pedometers (Accusplit, San Jose, California, USA) which assess purposeful steps taken. Pedometers were dispatched to all NAVIGATOR study centres and were supplied to a subset of participants based on practical considerations. Two weeks after the baseline visit, participants were fitted with a pedometer and instructed to wear it during waking hours for seven consecutive days. They were also provided with a log book to document their daily step count. Ambulatory activity levels were reassessed using the same criteria at yearly intervals. At each year, the pedometer activity level was summarised as the average over 7 days. Along with measure of habitual ambulatory activity, daily step counts also provide a reasonable measure of total physical activity levels.[14]

Statistical analysis

We undertook a longitudinal regression to evaluate pedometer steps as a predictor of future weight and subsequently reversing the relationship to evaluate weight as a predictor of future pedometer steps. Thus, the response variable, Y, was initially weight with independent variable, X, being pedometer steps. Then, this was reversed.

$$Y_{i,t} = \beta_0 + \beta_1 \times Y_{i,t-1} + \beta_2 \times Y_{i,t-2} + \beta_3 \times Y_{i,t-3} + \beta_4 \times \Delta X_{i,(t-2)\rightarrow(t-1)} + \beta_5 \times X_{i,t-2} + \underline{\beta_p} \times \underline{C_i}$$

where $Y_{i,t}$ is the the log-transformed response variable for individual i at time t, similarly defined for prior times t−1 (minus 1 year), t−2 (minus 2 years) and t−3 (minus 3 years). Log transformation was necessary to achieve normality for the response, for both weight and pedometer steps. We let $\Delta X_{i,(t-2)\rightarrow(t-1)}$ be the change in the predictor variable from time t−2 to t−1, $X_{i,t-2}$ is the predictor level at time t−2, and C_i index baseline covariates for the ith individual. Thus, the estimate of β_4 describes the association between changes in X (eg, pedometer counts) on subsequent values of the response Y (eg, weight), among people with a common history. β_4 and β_5 together describe the relationship between the history of X and subsequent Y after accounting for the prior history of Y.

Given the inclusion of lagged values of response as independent variables, the model could only be fit to response data starting at year 3. Only participants with response values at time t, preceded by three annual response values, at t−1, t−2, t−3 and a predictor value at t−1 and t−2 were included in the analysis. More lags were not considered because the number of patients contributing consecutive data points became small. However, responses at years 4, 5 and 6 were analysed as repeated measures, wherever available. Generalised estimating equations with a robust SE estimate were used to account for correlation from using multiple responses within individuals.

The analysis was conducted before and after adjustment for the following baseline characteristics: age, sex, race, region, smoking status, waist circumference, systolic blood pressure, pulse pressure, chronic obstructive pulmonary disease, atrial fibrillation/flutter, low-density lipoprotein and high-density lipoprotein cholesterol, platelets, haemoglobin, log of albumin/creatinine ratio, sodium, estimated glomerular filtration rate, ECG abnormalities, congestive heart failure, cerebrovascular disease, coronary heart disease, pulmonary disease, peripheral artery disease and family history of diabetes. Missing adjustment covariates were imputed; less than 3% of data were missing for baseline adjustment covariates.

Funding

NAVIGATOR was designed by an academic executive committee in collaboration with the sponsor, Novartis Pharmaceuticals, who funded the study. Statistical analyses were performed independently by statisticians at the Duke Clinical Research Institute (Durham, North Carolina, USA). The authors of this manuscript are solely responsible for the design and conduct of this study, all statistical analyses, and the drafting and editing of the paper and its final contents.

RESULTS

From the total NAVIGATOR population of 9306 individuals, 2811 had complete weight and physical activity data over the required time points. The baseline characteristics of those included in and excluded from the analysis are provided in table 1. Average age was 63 years, 50% were female and median weight at baseline was 80 kg. All models included 7318 data points from the 2811 participants; 755 participants contributed one data point, 546 contributed two data points, 569 contributed three data points and 941 contributed four data points. The median baseline step count was 6592 (IQR 4311–9334) steps per day. From baseline to the last recorded measurement in these 2811 individuals, step count fell by a median of 372 (IQR −2520 to 1651) steps per day while weight remained unchanged (median 0.0 kg (IQR −3.5 to 3.2 kg)).

Association of previous weight and recent change in weight with subsequent step count

Table 2 details the association of previous weight and recent change in weight with physical activity, after

Table 1 Baseline characteristics of NAVIGATOR participants

Variable	Included in analysis (n=2811)	Excluded from analysis (n=6495)
Age	63 (58–68)	63 (58–69)
Gender (female, %)	1418 (50.4)	3293 (50.7)
Race		
Caucasian	2243 (79.8)	5491 (84.5)
Asian	308 (11.0)	305 (4.7)
African–American	29 (1.0)	207 (3.2)
Other	231 (8.2)	492 (7.6)
Weight (kg)	80 (70–91)	83 (72–95)
Systolic BP (mm Hg)	140 (129–150)	139 (128–150)
Coronary heart disease	835 (29.7)	1791 (27.6)
Cerebrovascular disease	259 (9.2)	477 (7.3)
Congestive heart failure	124 (4.4)	207 (3.2)
Peripheral arterial disease	70 (2.5)	239 (3.7)
Chronic obstructive pulmonary disease	114 (4.1)	337 (5.2)

Values are median (IQR) or n (%).
BP, blood pressure; NAVIGATOR, Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research.

adjusting for the previous trajectory of physical activity. Previous weight was inversely associated with subsequent step count, indicating lower subsequent levels of physical activity in heavier individuals. When expressed in absolute terms, however, every 1 kg higher weight was associated with only 0.21% fewer steps in the subsequent year of measurement in otherwise similar individuals (table 2). For example, in two otherwise similar individuals with a daily step count of approximately 10 000/day, a 10 kg heavier person would walk only 220 fewer steps per day, in the subsequent year. This limited clinical impact was reflected by the finding that the adjusted R^2 for prior step count and weight data was only marginally different from the adjusted R^2 for only prior step count (0.5882 vs 0.5895) in its association with subsequent step count, that is, weight data only explained 0.13% of the variance in subsequent step count. Change in weight was not associated with subsequent step count in the model (p=0.71). The previous trajectory of physical activity was strongly associated with subsequent physical activity levels as expected.

Association of previous step count and recent change in step count with weight

Table 3 details the association of previous step count and recent change in step count with subsequent weight, after adjusting for the previous trajectory of weight. Step count at a previous visit was not associated with subsequent weight (p=0.34), but change in step count was inversely associated with subsequent weight in the model. When expressed in absolute terms, however, every additional 2000 steps were associated with only 0.08% lower weight at the subsequent study visit in otherwise similar individuals (table 3). Among two otherwise similar individuals weighing 80 kg, a 2000 increase in daily step count was associated with only 60 g lower weight at the subsequent visit. This limited clinical impact was reflected by the finding that the adjusted R^2 for prior weight and step count data was similar to the adjusted R^2 for only prior weight (0.9651 vs 0.9652) in its association with subsequent weight, that is, step count data only explained 0.01% of the variance in subsequent weight. The previous trajectory of weight was strongly associated with subsequent weight as expected.

DISCUSSION

In 2811 NAVIGATOR participants with IGT who underwent regular objective measurements of weight and physical activity, the following findings relating to the bidirectional nature of the prospective associations between these variables emerged. Previous weight, but not recent change in weight, was inversely associated with subsequent levels of physical activity. Recent change in physical activity, but not previous physical activity, was inversely associated with subsequent weight. However, the relative contributions of weight to subsequent physical activity and of physical activity to subsequent weight, while statistically significant, were of somewhat limited clinical importance. Previous physical activity was very strongly associated with subsequent activity and, similarly, previous weight with subsequent weight but addition of weight and physical activity data, respectively, had negligible effect on prediction of the other.

Previous studies have investigated the prospective relationships between weight and physical activity with a variety of approaches and also suggested that any link is very modest. In an observational analysis of the Womens' Health Study (n=34 079), participants gained an average of 2.6 kg over 13 years.[15] Those who were least active at baseline gained only 0.12 kg more weight than the most active participants over 3 years. Importantly, both weight and physical activity were self-reported. In a study of 288 498 participants in the European Prospective Investigation into Cancer and Nutrition which included baseline self-reporting of activity (inactive, moderately inactive, moderately active and active categories) plus baseline and follow-up objective measurement of weight and waist circumference, physical activity had no relationship with subsequent weight.[16] A single category increment in activity only led to 0.4–0.5 mm/year smaller waist circumference. The association between baseline weight and future activity was not investigated in these studies.

Table 2 Associations of previous step count, previous weight and recent change in weight with subsequent step count (adjusted model)

Parameter	Estimate	SE	χ^2	p Value	Joint effects
Log step count (t–3)	0.1175	0.0169	41.9	<0.0001	432.6
Log step count (t–2)	0.2263	0.0194	98.2	<0.0001	(p<0.0001)
Log step count (t–1)	0.5045	0.0197	320.6	<0.0001	
Weight (t–2)	−0.0021	0.0005	16.8	<0.0001	17.8
Change in weight (t–1)	−0.0028	0.0018	0.1	0.71	(p=0.0001)

Adjusted for step count values from last three annual visits (t–1, t–2, t–3) and baseline covariates (age, sex, race, region, smoking status, waist circumference, systolic blood pressure, pulse pressure, chronic obstructive pulmonary disease, atrial fibrillation/flutter, low-density lipoprotein and high-density lipoprotein cholesterol, platelets, haemoglobin, log of albumin/creatinine ratio, sodium, estimated glomerular filtration rate, ECG abnormalities, congestive heart failure, cerebrovascular disease, coronary heart disease, pulmonary disease, peripheral artery disease and family history of diabetes).
Weight expressed per kg and step count per 2000 steps.

Table 3 Associations of previous weight, previous step count and recent change in step count with subsequent weight (adjusted model)

Parameter	Estimate	SE	χ^2	p Value	Joint effects
Log (weight (t–3))	0.0885	0.0123	46.8	<0.0001	747.3
Log (weight (t–2))	0.1339	0.0183	43.0	<0.0001	(p<0.0001)
Log (weight (t–1))	0.7638	0.0191	484.9	<0.0001	
Step count (t–2)	–0.0003	0.0003	0.9	0.34	5.9
Change in step count (t–1)	–0.0008	0.0003	5.9	0.02	(p=0.05)

Adjusted for weight values from last three annual visits (t–1, t–2, t–3) and baseline covariates (age, sex, race, region, smoking status, waist circumference, systolic blood pressure, pulse pressure, chronic obstructive pulmonary disease, atrial fibrillation/flutter, low-density lipoprotein and high-density lipoprotein cholesterol, platelets, haemoglobin, log of albumin/creatinine ratio, sodium, estimated glomerular filtration rate, ECG abnormalities, congestive heart failure, cerebrovascular disease, coronary heart disease, pulmonary disease, peripheral artery disease and family history of diabetes).
Weight expressed per kg and step count per 2000 steps.

However, the majority of studies have suggested that previous weight is a determinant of subsequent physical activity. In an observational Danish study of 6279 adults who attended three study visits over 10 years, the investigators found no difference in the risk of developing obesity according to levels of physical activity at baseline.[4] In contrast, those with high body mass index (BMI) were at elevated risk of becoming inactive compared with those with median BMI. A similar study from the same research group of 1143 obese adults and 1278 non-obese controls yielded similar results.[5] While weight was objectively measured, categories of physical activity were again recorded by self-report questionnaire. The Medical Research Council Ely Study followed up 393 middle-aged adults for 5.6 years and analysed data for objectively measured weight and activity levels (derived from heart rate monitor data), recorded at two visits, in a further observational study.[6] Here, baseline sedentary time did not predict any subsequent measures of adiposity but most baseline measures of adiposity were positively associated with subsequent sedentary time. In the University of North Carolina Alumni Heart Study of 4595 men and women, studied from age 41 to 54, BMI was again positively associated with the risk of becoming sedentary.[7] Sedentary lifestyle did not predict change in subsequent BMI, a finding replicated in other studies.[17] However, a positive association with adiposity did emerge from their statistical model when change in physical activity was added as a variable. Two interesting small intervention studies have further supported the hypothesis that weight change is a determinant of subsequent physical activity. In Levine *et al*'s[18] study of lean (n=10) and obese (n=12) participants who were overfed by 1,000 kcal/day for 8 weeks and who gained 3.6 kg in weight from this experimentally induced overfeeding, both groups walked approximately 1.5 miles/day less (objectively measured) after the intervention. Bonomi *et al* used an alternative approach by exposing 66 overweight or obese participants to a 67% energy restricted diet for 6 weeks. Participants lost weight and this was associated with a subsequent increase in physical activity recorded with triaxial accelerometers.[19] By contrast, a study in which 25 adults were overfed (140% of energy needs) for 8 weeks led to increases in activity and energy expended in physical activity.[20] However, these studies were conducted over relatively short periods of time and therefore assess acute changes in behaviour, rather than the longer term effects investigated in the present study.

The current results largely support these earlier findings and add further information regarding the magnitude of the associations between weight and activity. While the findings from NAVIGATOR generally support the hypothesis that there is a bidirectional prospective relationship between weight and physical activity which provides important and novel insights into the nature of these associations, an important conclusion was that the magnitude of these associations was of limited clinical importance, in the context of the changes observed in this observational analysis. Therefore, in clinical terms, it appears important to both directly target increasing activity, primarily for its associated benefits independent of weight loss (eg, improved insulin sensitivity, blood pressure, lipoprotein metabolism, vascular function[21])—as weight loss may have a limited effect on habitual activity—and to directly target weight loss, through dietary restriction, rather than via increased physical activity, as increased natural variation in physical activity may have limited effect on weight. Although life-long activity may contribute to weight and vice versa, natural variation in these parameters, after diagnosis with IGT, appears too small to signal a new trajectory. Instead it is dwarfed by the trajectory that has already been established.

Strengths of this analysis of the NAVIGATOR cohort include the large number of participants from whom objective measures of both weight and physical activity were available. Data from multiple time points also allowed us to study the potential relationships between weight and activity beyond the trajectories already established for these variables within individuals. Participants were well phenotyped at baseline and, importantly, all had IGT, a condition associated with very high risk of progression to type 2 diabetes and therefore a clinically relevant group in which to study the relationship

between activity and weight. Weaknesses of our study include that this was an observational analysis and therefore not able to provide information on causal relationships. Given the non-randomised nature of this study and moderate effect sizes, it is possible for unmeasured confounding to explain the associations. However, this is unlikely to substantially alter our conclusion that the associations do not suggest a strong relationship. In addition, our analysis does not evaluate life-long causal relationships, but only the most recent variations in the predictor, after adjusting for the response trajectory that has already been established. In observational data, this is as close as can be achieved for blocking reverse causation. However, among people with a similar response trajectory, there may be relatively little variation in predictor values. Therefore, our conclusions do not generalise to an intervention that could induce much greater differences between individuals than are seen in natural behaviour. Participants were followed for variable periods of time and therefore contributed variable numbers of data points with the result that data from only 30% of NAVIGATOR participants were considered adequate for our analytical approach. We used step count as a measure of physical activity which does not provide information on intensity. This may have limited our ability to detect any associations between moderate-to-vigorous physical activity and body weight. While we analysed our data according to the principles of Granger causation, other approaches such as latent growth curve modelling have been applied to such longitudinal data.[22] As the design of the analysis precluded a comparison group, we were unable to take into consideration the natural trajectories of changes in activity and weight in such individuals. Finally, our participants were relatively old with IGT and at high risk of cardiovascular disease, and thus our findings may not be generalisable to all groups.

In summary, while we observed inverse associations between previous weight and subsequent physical activity plus recent change in physical activity and subsequent weight, in keeping with a bidirectional relationship, the magnitude of these associations was of limited clinical significance.

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Acknowledgements NAVIGATOR was designed by an academic executive committee in collaboration with the sponsor, Novartis Pharmaceuticals, who funded the trial. Statistical analyses were performed independently by statisticians at the Duke Clinical Research Institute (DCRI; Durham, North Carolina, USA).

Contributors DP, SMH, JMRG, TY, MJD and WEK designed this analysis of the NAVIGATOR study. SMH, RRH, JJM and RMC designed and performed the original NAVIGATOR study and contributed to the design of this project. LET and DMW conducted the statistical analyses. DP and JMRG wrote the first draft and all authors were involved in reviewing and editing the manuscript. All authors read and approved the final manuscript.

Funding NAVIGATOR was funded by Novartis; this analysis was conducted independently at DCRI.

Competing interests None declared.

Ethics approval Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The randomised trial data are held by DCRI and by Novartis. These analyses were performed independently by DCRI.

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BMJ Open 2015 5:
doi: 10.1136/bmjopen-2015-007901