Nutrition, Metabolism & Cardiovascular Diseases (2018) **28**, 243–251

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Trajectories of BMI change impact glucose and insulin metabolism

E.I. Walsh [a,*], J. Shaw [b], N. Cherbuin [a]

[a] Centre for Research on Ageing, Health and Wellbeing, Australian National University, Canberra, Australia
[b] Baker Heart & Diabetes Institute, Melbourne, Australia

Received 9 October 2017; received in revised form 4 December 2017; accepted 6 December 2017
Handling Editor: Peter Clifton
Available online 15 December 2017

KEYWORDS
Weight change;
Insulin;
HOMA;
Glucose;
Body Mass Index

Abstract *Background and aims:* The aim of this study was to examine, in a community setting, whether trajectory of weight change over twelve years is associated with glucose and insulin metabolism at twelve years.
Methods and results: Participants were 532 community-living middle-aged and elderly adults from the Personality and Total Health (PATH) Through Life study. They spanned the full weight range (underweight/normal/overweight/obese). Latent class analysis and multivariate generalised linear models were used to investigate the association of Body Mass Index (BMI, kg/m^2) trajectory over twelve years with plasma insulin (μlU/ml), plasma glucose (mmol/L), and HOMA2 insulin resistance and beta cell function at follow-up. All models were adjusted for age, gender, hypertension, pre-clinical diabetes status (normal fasting glucose or impaired fasting glucose) and physical activity. Four weight trajectories were extracted; constant normal (mean baseline BMI = 25; follow-up BMI = 25), constant high (mean baseline BMI = 36; follow-up BMI = 37), increase (mean baseline BMI = 26; follow-up BMI = 32) and decrease (mean baseline BMI = 34; follow-up BMI = 28). At any given current BMI, individuals in the constant high and increase trajectories had significantly higher plasma insulin, greater insulin resistance, and higher beta cell function than those in the constant normal trajectory. Individuals in the decrease trajectory did not differ from the constant normal trajectory. Current BMI significantly interacted with preceding BMI trajectory in its association with plasma insulin, insulin resistance, and beta cell function.
Conclusion: The trajectory of preceding weight has an independent effect on blood glucose metabolism beyond body weight measured at any given point in time.

Introduction

Adiposity is associated with elevated blood glucose levels, insulin resistance, and is a risk factor for the development of type 2 diabetes [1–4]. Moreover, weight gain over a period of several years is associated with elevated blood glucose, insulin resistance, and increased risk of diabetes [1,5]. Conversely, weight loss can improve glycaemic control and insulin sensitivity in individuals with or without diabetes [6,7]. Current or momentary weight (e.g. weight measured at any given point in time) and preceding weight change can have simultaneous, independent effects on cardiovascular risk outcomes [8], hypertension [9], and insulin and glucose metabolism [10–12]. However, the extent to which momentary Body Mass Index (BMI, kg/m^2) interacts with BMI change trajectories and predicts insulin secretion and sensitivity has not yet been clearly established.

* Corresponding author. Centre for Research on Ageing, Health and Wellbeing, 54 Mills Road, Australian National University, Acton, ACT, 2601, Australia.
E-mail address: erin.walsh@anu.edu.au (E.I. Walsh).

https://doi.org/10.1016/j.numecd.2017.12.003
0939-4753/

Generalizability of extant research on this topic is limited by sample (e.g. solely women in Jernström and Barratt-Conner [10]; solely obese individuals in Sjöholm et al. [12]) or operationalisation of glucose and insulin metabolism (e.g. only fasting insulin in Norman et al. [11]). Yet, taken together, they suggest that weight change over a number of years may have an effect independent of current weight on glucose and insulin metabolism. There is some evidence that insulin resistance that develops as a consequence of obesity can prevent additional weight gain [13,14]. Therefore, greater insulin resistance may be expected in an individual with consistently high weight than in an individual gaining weight, even if they have the same weight at the time of measurement. Ferrannini et al. (2004) [15] found that hypersecretion of insulin associated with obesity does not diminish following weight loss. Therefore, higher insulin production (and consequently higher plasma insulin concentration) could be expected in an individual who had previously lost weight rather than an individual with consistently low weight, again even if weight is the same at the time of measurement. Understanding potentially distinct properties of insulin metabolism associated with these different trajectories is important, because changes in insulin metabolism precede and determine changes in blood glucose and diabetes onset [16]. The objective of this study was therefore to address these substantive questions by examining the relationship between trajectories of weight change over twelve years and blood glucose, plasma insulin, insulin sensitivity, resistance and beta cell function in a large sample of community-living middle aged and older adults spanning the typical weight range observed in the community.

Methods

Study population

Participants were sampled from the Personality and Total Health (PATH) Through Life study, a large longitudinal study investigating ageing, health, cognition and other individual characteristics over the course of twelve years. As described in Anstey et al. (2012) [17], participants living in Canberra or Queanbeyan were randomly recruited from the electoral roll. Voting is compulsory in Australia. There are currently four waves of data collection, with measures taken every four years.

From the full PATH cohort of 7485 participants, the current study was concerned with cohorts aged 40–45 at baseline and 60–65 at baseline (40s $n = 2530$; 60s $n = 2551$; $N = 5081$). A random subsample of participants was selected for blood measures at each of the four follow-up occasions (remaining 40s $n = 247$, 60s $n = 433$; $N = 680$). From these, participants were selected on the basis of successful extraction of insulin levels from blood (remaining 40s $n = 242$, 60s $n = 429$; $N = 671$), and BMI measures available at two or more waves to allow calculation of BMI trajectories, (remaining 40s $n = 237$, 60s $n = 427$; $N = 664$). To clarify results in relation to the complex the association between dementia and insulin [18], participants were also excluded if they had and any history of dementia or an MMSE score of less than 26 [19] at any point in the study (remaining 40s $n = 242$, 60s n = 370). Finally, participants with diagnosed T2D at any point in the study were excluded, resulting in a final sample size of 532 (40s $n = 224$, 60s $n = 308$). Approval for the study was obtained from the human research ethics committees of the Australian National University (protocol number: wave 1 M9807; wave 2 2002/189; wave 3 2006/314; wave 4 2010/542) and the University of New South Wales (HREC 00149).

Blood measures

Venous blood was collected following an overnight fast of at least 10 h. Plasma glucose (mmol/L) was measured on a Beckman LX20 Analyzer by an oxygen rate method (Fullerton, California). Plasma insulin (μlU/ml) and C-peptide (pmol/l) were measured via enzyme-linked immunosorbent assay (ELISA), averaged across 2 samples from each participant. These measured were used to calculate insulin resistance (HOMA2-IR), sensitivity (HOMA2-%S), and production (β cell function, HOMA2-%β) using the computer Homeostatic model assessment outlined in Wallace, Levy, and Matthews (2004) [20].

Body Mass Index

BMI was computed with the formula weight (kg)/height^2 (m^2) based on self-report of weight and height.

Covariates

Participants were considered hypertensive based on self-reported medication use, or the average of two seated blood pressure measures exceeding 140 mmHg systolic and 90 mmHg diastolic. To adjust for the possible impact of pre-clinical high blood glucose levels on insulin function, a variable was created to reflect categories of IFG (not type 2 diabetes and two or more blood glucose measures >5.6 mmol/L), or NFG (not type 2 diabetes or IFG, and two or more blood glucose measures <5.6) [21]. Physical activity was measured in term of Metabolic Equivalents (METs), from self-reported hours spent engaging physical using the formula (hours mild PA × 3) + (hours moderate PA × 6) + (hours vigorous PA × 9) [22].

Statistical analyses

All analyses were carried out in R version 3.2.0. α was set at 0.05. Sampling bias (selected/not selected) and drop out (measures available/not available at final wave) were investigated with t and chi square tests. Possible multivariate outliers were detected via Mahalanobis distances exceeding 20 (chi square cut-off at $\alpha = 0.05$, at 11 degrees of freedom for 5 DVs, 2 IVs, and covariates).

Missingness

There was no missingness in insulin, and 2.02% of BMI data were missing (though no more than one missing occasion for each participant). Of a total of 2128 data points (532 participants × four measurement occasions), <1% of covariate data was missing. To preserve sample size, this missing data in covariates was singly imputed in SPSS version 22, EM at 1000 iterations.

Trajectories

A latent class model was used to estimate mutually exclusive classes of BMI change over time. Exploratory modelling and the Bootstrap Likelihood Ratio Test (BLRT) were used to establish the appropriate number of classes (2, 3, 4, or 5) and link function (linear, or beta), using the packages mclust (version 5.2) and lcmm (version 1.7.5).

Multivariate generalised linear models

Multivariate generalised linear models were applied to account for relatedness between the outcome measures. Plasma glucose, plasma insulin, HOMA2-IR, HOMA2-%β and HOMA2-%S were specified as outcome variables, and follow-up BMI, BMI class, and covariates were specified as predictors. If multivariate significance (indicated by F-statistic derived from the Pillai-Bartlett Trace) was achieved, general linear models for each outcome were computed. Three models were fit: (1) the impact of BMI (at wave 4) on outcomes, (2) the impact of trajectory on plasma glucose, insulin, HOMA2-IR, HOMA2-%β and HOMA2-%S, then (3) the interaction between BMI (at wave 4) and trajectory on plasma glucose, insulin, HOMA2-IR, HOMA2-%β and HOMA2-%S.

Results

Participant characteristics are displayed in Table 1. t and χ^2 tests revealed no significant difference between selected/not selected in gender, physical activity, blood glucose at wave 4, or hypertension. However those included were significantly older ($t(667.419) = -4.224$, $p < 0.05$ (M = 53 vs M = 55)). Latent class analysis resulted in four BMI trajectories which are henceforth referred to as constant normal, constant high, increase, and decrease (summarised in Fig. 1) as these best described the patterns of change observed. It should be noted however that "constant normal" does include a minority of participants who over the follow-up can be categorised as overweight but since sensitivity analyses (see below) indicate that these participants did not meaningfully influence the pattern of results they were kept in this group to maintain the integrity of the analytical approach used. Trajectories were similar between age groups.

In the 40s cohort, baseline BMI was 25.51 kg/m^2 (SD = 3.33) in the constant normal trajectory, 37.17 kg/m^2 (SD = 2.97) in constant high, 24.86 kg/m^2 (SD = 3.1) in increase, and 31.96 kg/m^2 (SD = 3.55) in the decrease trajectory. BMI increase between baseline and final follow-up was almost ubiquitous, with constant normal ($t = 8.09$, $p < 0.01$), constant high ($t = 3.93$, $p < 0.01$), and increase ($t = 14.79$, $p < 0.01$) all significantly increasing in BMI, and only decrease ($t = -8.05$, $p < 0.01$) significantly decreasing in BMI (for more detail, see supplementary materials).

In the 60s cohort, baseline BMI was 24.91 kg/m^2 (SD = 3.03) in the constant normal trajectory, 36.60 kg/m^2 (SD = 2.60) in constant high, 26.55 kg/m^2 (SD = 4.66) in increase, and 34.51 kg/m^2 (SD = 2.72) in the decrease trajectory. Neither the constant normal ($t = 0.14$, $p = 0.89$) nor constant high ($t = 0.24$, $p = 0.80$) underwent significant change in BMI between baseline and final follow-up, while decrease ($t = -4.77$, $p < 0.01$) and increase

Table 1 Descriptive statistics.

Variable	All participants				40s cohort				60s cohort			
	M	SD	Min	Max	M	SD	Min	Max	M	SD	Min	Max
Age (wave 4)	67.14	9.82	53.17	78.54	55.75	1.39	53.17	58.35	75.42	1.44	72.85	78.54
Goldberg (wave 4)	1.81	2.05	0	9	2.25	2.4	0	9	1.49	1.69	0	8
METs (wave 4)	49.98	46.05	0	345	42.46	2.82	0	345	55.37	47.57	0	279
Insulin (wave 4)	14.33	11.53	0.77	70.93	17.04	12.85	1.02	70.93	12.35	10.05	0.77	68.52
Plasma Glucose (wave 4)	5.21	0.63	3.4	8.2	5.18	0.61	3.4	8.2	5.23	0.64	3.8	7.8
HOMA2 IR (wave 4)	1.81	1.37	0.1	6.76	2.13	1.5	0.13	6.76	1.58	1.23	0.1	6.54
HOMA2 %β (wave 4)	105.68	33.16	44.9	302.4	104.4	33.94	47.4	260	106.62	32.6	44.9	302.4
HOMA2 %S (wave 4)	104.38	98.71	14.8	976.7	87.03	83.75	14.8	768.1	116.96	106.66	15.3	976.7
BMI (wave 1)	25.97	4.19	17.2	43.51	26.42	4.32	19.1	43.51	25.64	4.06	17.2	41.47
BMI (wave 4)	26.49	4.44	16.79	43.51	27.45	4.63	16.79	43.51	25.79	4.17	17.61	40.09
BMI change per year (% of wave 1 BMI)	0.04	(0.16%)			0.09	(0.34%)			0.01	(0.04%)		
Gender, *n* Male (% Male)	268	(50.38%)			103	(45.98%)			165	(53.57%)	165	
n with IFG (% IFG)	95	(17.86%)			34	(15.18%)			61	(19.81%)	61	
Sample N	532				224					308		

Note: Change in BMI per year (absolute and percentage) was calculated from a linear model, with time as a predictor of change. IFG = Impaired fasting glucose.

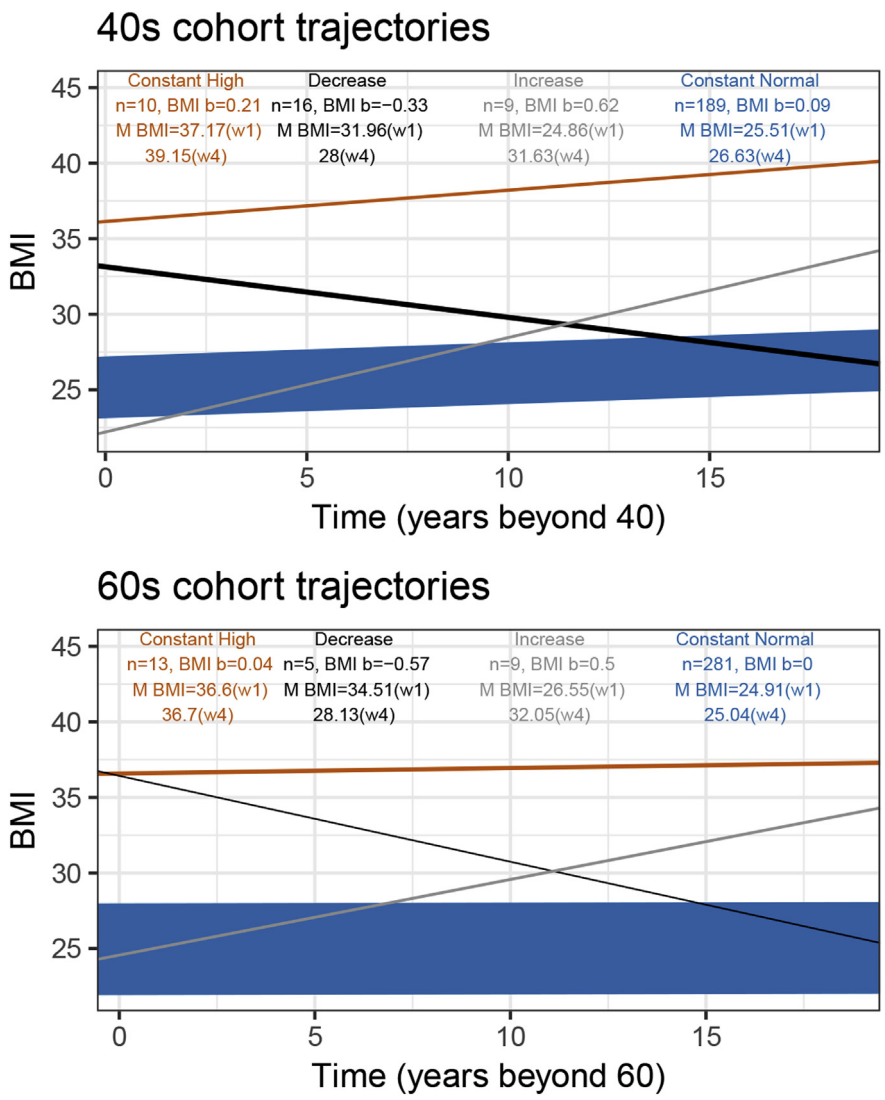

Figure 1 Trajectories extracted via latent class analysis. *Note*: "Time" is age of each cohort centred at minimum age at wave 1 (40 for 40s cohort, 60 for 60s cohort). Line intercept and slope are drawn from a hierarchical linear model for each trajectory, with time as sole predictor of BMI. Line weight and n in annotation corresponds to number of participants per class, b corresponds to the change in BMI per unit time (year beyond minimum age at wave 1). "M BMI" denotes mean BMI for each trajectory. The exploratory modelling and the Bootstrap Likelihood Ratio Test indicated either a three or four class solution was optimal. Further investigation of power available to subsequent analyses (Cohen's f, calculated given the size of the smallest category, power of 0.8, and alpha of 0.05 using pwr, version 1.1–3) indicated little difference in power afforded by three and four classes for either 40s (from 0.30 to 0.28) or 60s (from 0.23 to 0.22). Four classes were chosen due to the theoretical relevance of categories of constant high, increase, decrease, and constant normal.

($t = 9.27$, $p < 0.01$) significantly changed in their respective directions.

Constant normal was used as the reference group for comparison in analyses. Results for the impact of trajectory, and interaction between BMI at wave 4 and trajectory are summarised visually in Fig. 2 and reported in Table 2. In both cohorts, higher BMI at wave 4 was significantly associated with higher plasma insulin at wave 4, increased insulin resistance at wave 4, higher beta cell function, and lower insulin sensitivity (Table 3).

Constant high trajectory

In the 40s cohort, the constant high trajectory was associated with significantly higher plasma insulin ($M = 27.74$ μlU/ml vs $M = 16.63$ μlU/ml) insulin resistance ($M = 3.51\%$ vs $M = 2.02\%$), and beta cell function ($M = 131.55\%$ vs $M = 102.09\%$), than constant normal. In fully adjusted models, at any given BMI, plasma insulin was 107% higher ($p < 0.01$), insulin resistance 104% greater ($p < 0.01$), and beta cell function 28% higher ($p < 0.01$) if preceded by high rather than normal trajectory. Preceding trajectory also significantly interacted with current BMI for these outcomes, such that the impact of each unit of BMI was 20% greater on plasma insulin ($p = 0.01$) and 19% greater on insulin resistance ($p = 0.02$) in the constant high than in the constant normal trajectory. In the 60s cohort, the constant high trajectory was significantly associated with higher plasma insulin ($M = 19.84$ μlU/ml vs $M = 12.62$ μlU/ml) and insulin resistance ($M = 2.73\%$ vs $M = 1.61\%$), such that, in

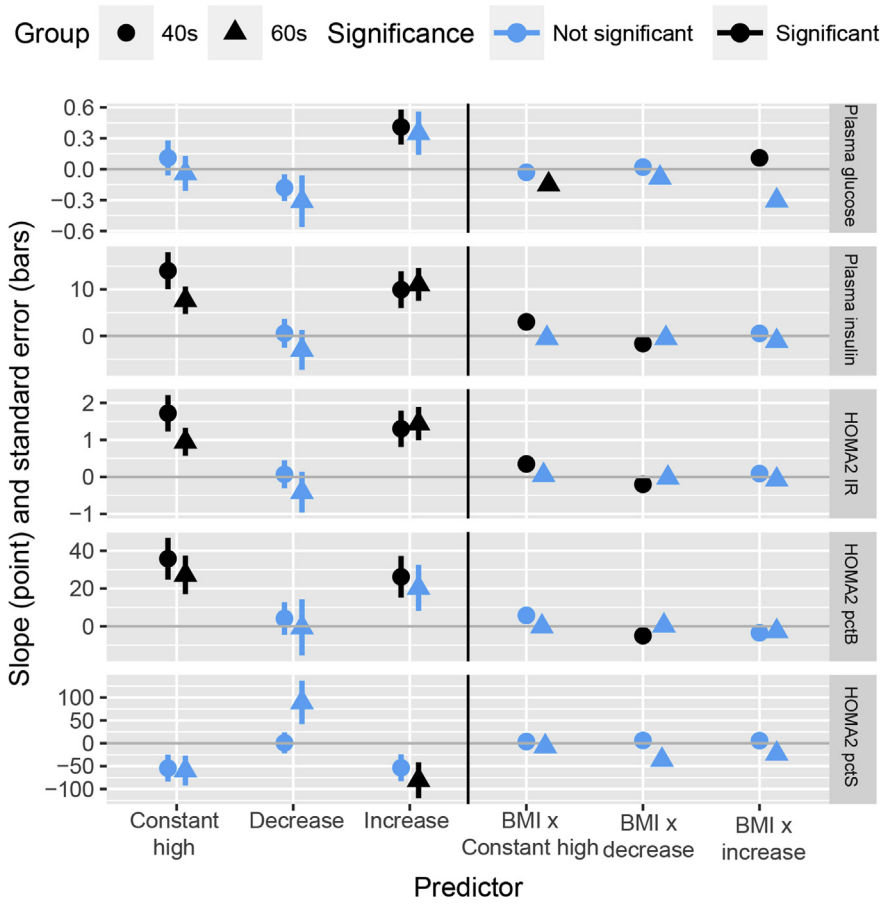

Figure 2 Multivariate analysis results. *Note*: Points indicate slope in fully controlled post-hoc linear model, with grey line indicating zero (so points below line indicate negative association, points above line indicate positive association). Error bars represent standard error from the same model. Significance is at $\alpha < 0.05$.

fully adjusted models and at any given BMI, plasma insulin was 40% higher ($p = 0.01$), and insulin resistance 40% greater ($p = 0.03$) if preceded by high rather than normal trajectory. There was a significant interaction between BMI and plasma glucose, such that those in the constant high trajectory experienced 0.12 mmol/L lower blood glucose associated with each unit increase in BMI.

Decrease trajectory

In the 40s cohort, the decrease trajectory alone was not significantly associated with any blood measure, but preceding trajectory significantly interacted with BMI, such that the impact of each unit of BMI was 11% less ($p = 0.02$) on plasma insulin, 10.92% less ($p = 0.02$) on insulin resistance, and 4% less beta cell function ($p = 0.01$) relative to constant normal trajectory. In the 60s cohort, there were no significant differences between the decrease and constant normal trajectories. However, individuals in the decrease trajectory had significantly better outcomes (e.g. lower plasma glucose, insulin resistance, etc.) when compared to the constant high trajectory (40s Pillai = 0.16, $F(15/606) = 2.4$, $p < 0.01$; 60s Pillai = 0.15, $F(15/633) = 2.3$, $p < 0.01$).

Increase trajectory

In both cohorts, the increase trajectory was significantly associated with higher plasma insulin (40s $M = 23.74$ μlU/ml vs $M = 16.63$ μlU/ml; 60s $M = 23.68$ vs $M = 11.71$), insulin resistance (40s $M = 3.07\%$ vs $M = 2.07\%$; 60s $M = 3.13\%$ vs $M = 1.49\%$), and in the 40s, beta cell function (40s $M = 126.11$ vs $M = 102.09$; 60s $M = 114.38$ vs $M = 105.16$). In fully adjusted models, at any given BMI, and in comparison to the constant normal trajectory, the increase trajectory was associated with 76% (40s; $p = 0.01$) or 77% (60s; $p < 0.01$) higher plasma insulin, 79% (40s; $p = 0.01$) or 39% (60s; $p < 0.01$) greater insulin resistance, and 21% (40s; $p = 0.02$) or 13.45% (60s; $p = 0.01$) higher beta cell function. In the 40s cohort, preceding increase trajectory significantly interacted with plasma glucose, such that the impact of each unit of BMI was 2.21% greater relative to constant normal trajectory.

Sensitivity analysis

Potential bias from covariates was investigated by fitting multiple models from unadjusted to fully adjusted (age,

Table 2 Multivariate significance.

Outcome	Predictor	40s			60s		
	—	F	Pillai	p	F	Pillai	p
Model (1)							
	(Intercept)	F(5200) = 11,520.42	1	<0.01	F(5211) = 11,207.35	1	<0.01
	BMI	F(5200) = 35.97	0.41	<0.01	F(5211) = 16.83	0.29	<0.01
	Age	F(5200) = 0.43	0.01	0.87	F(5211) = 0.77	0.02	0.58
	Gender	F(5200) = 5.72	0.13	<0.01	F(5211) = 2.98	0.07	0.01
	PA	F(5200) = 1.05	0.03	0.39	F(5211) = 0.54	0.01	0.75
	IFG	F(5200) = 12.09	0.23	<0.01	F(10,424) = 8.2	0.32	<0.01
	Hypertension	F(5200) = 1.84	0.04	0.11	F(5211) = 0.29	0	0.92
Model (2)							
	(Intercept)	F(5200) = 10,886.73	1	<0.01	F(5255) = 5563.97	0.99	<0.01
	Trajectory	F(15,606) = 2.35	0.17	<0.01	F(15,771) = 4.78	0.26	<0.01
	Age	F(5200) = 0.51	0.01	0.77	F(5255) = 1.5	0.03	0.19
	Gender	F(5200) = 8.08	0.17	<0.01	F(5255) = 3.18	0.06	0.01
	PA	F(5200) = 1.6	0.04	0.16	F(5255) = 1.03	0.02	0.4
	IFG	F(5200) = 13.87	0.26	<0.01	F(10,512) = 15.61	0.47	<0.01
	Hypertension	F(5200) = 3.02	0.07	0.01	F(5255) = 0.2	0	0.96
Model (3)							
	(Intercept)	F(5194) = 11,906.4	1	<0.01	F(5205) = 11,132	1	<0.01
	BMI	F(5194) = 39.52	0.50	<0.01	F(5205) = 17.87	0.35	<0.01
	Trajectory	F(15,588) = 2.13	0.16	<0.01	F(15,621) = 2.18	0.15	<0.01
	Age	F(5194) = 0.58	0.01	0.71	F(5205) = 0.61	0.01	0.69
	Gender	F(5194) = 4.74	0.04	0.11	F(5205) = 2.18	0.05	0.06
	PA	F(5194) = 1.01	0.03	0.41	F(5205) = 0.49	0.01	0.78
	IFG	F(5194) = 12.82	0.25	<0.01	F(10,412) = 7.71	0.32	<0.01
	Hypertension	F(5194) = 1.94	0.05	0.09	F(5205) = 0.3	0.01	0.91
	BMI*Traj	F(15,588) = 2.5	0.18	<0.01	F(15,621) = 1.46	0.11	0.11

Note: While individual linear models can be fit to examine each outcome in isolation, multivariate significance is informative given it is anticipated that the outcomes will be correlated with one another. Accordingly, all outcomes (plasma glucose, insulin, HOMA2-IR, HOMA2-%β and HOMA2-%S) were examined in the same multivariate model, and multivariate significance examined via F-statistic derived from the Pillai-Bartlett Trace. Significance indicates that some or all of the outcomes are significantly associated with predictors, even when correlation between outcomes is accounted for. Three models were fit: (1) the impact of BMI (at wave 4) on outcomes, (2) the impact of trajectory on outcomes, then (3) the interaction between BMI (at wave 4) and trajectory on outcomes. All models adjust for age, gender, hypertension, pre-clinical diabetes status (base group for comparison is normal fasting glucose, IFG = impaired fasting glucose), and physical activity.

gender, physical activity, impaired fasting glucose, and hypertension) and excluding potential multivariate outliers (11 excluded from 40s, 17 excluded from 60s). As summarised in Supplementary Figs. D and E, coefficient directionality and significance was generally consistent. The pattern of significance across models in the 40s indicates that the significant association between BMI and plasma glucose may be due to outliers (as it is not significant in an unadjusted model, or where outliers are excluded). Further analyses were conducted for a broader sample that included individuals with T2D, adding 13 individuals to the 40s, and 62 individuals to the 60s cohorts thus increasing the total sample size to 607. Results (including trajectories and multivariate results) were very similar (see supplementary materials for further details). While all individuals in the constant high trajectory had BMI $>$ 30 at all times, due to some waves with BMI increase followed by decrease the next wave, there was some overlap in range with the constant normal trajectories (43 individuals in the 40s and 38 in the 60s in the constant normal trajectory have a BMI $>$ 30 at one or more points). Analyses were repeated with these individuals excluded. Coefficient direction, magnitude, and significance was unaffected by this.

Discussion

We examined the impact of body weight and preceding weight change trajectories over twelve years on blood glucose, insulin, and HOMA2 measures of insulin metabolism. Unsurprisingly, results support the conclusion that high body weight is associated with elevated blood glucose levels and impaired insulin function [1–4]. Of much greater interest however, are the novel findings indicating that naturalistic weight change (rather than change induced by dietary or surgical intervention in a particular at-risk population) is associated with insulin metabolism in adult humans, and that trajectories of weight gain and high weight maintenance have distinguishable impacts on insulin metabolism.

Our findings that individuals with a high BMI and following a stable trajectory have a higher beta cell function is consistent with previous research indicating that obesity is associated with an adaptive increase in beta cell function [23]. Further, this is the first longitudinal cohort study of community-living adults to address the proposition that increase in body mass initially increases demand on beta cells (hence implying increased beta cell mass and function), but this is then decreased with continued high

Table 3 Multivariate analysis results.

Outcome	Predictor	40s			60s		
		b	SE	p	b	SE	p
Model (1)							
Plasma glucose	(Intercept)	4.29	0.38	<0.01	4.74	0.53	<0.01
	BMI	0.03	0.01	0.16	0.02	0.01	0.02
	Adj R^2	0.36			0.34		
Plasma insulin	(Intercept)	12.3	8.25	0.14	11.13	8.42	0.19
	BMI	1.33	0.16	<0.01	1	0.14	<0.01
	Adj R^2	0.27			0.22		
HOMA2 IR	(Intercept)	1.54	1.02	0.13	1.41	1.08	0.2
	BMI	0.17	0.02	<0.01	0.13	0.02	<0.01
	Adj R^2	0.29			0.22		
HOMA2 %β	(Intercept)	124.62	23.58	<0.01	130.88	29.37	<0.01
	BMI	3.34	0.45	<0.01	3.09	0.49	<0.01
	Adj R^2	0.24			0.18		
HOMA2 %S	(Intercept)	120.35	63.55	0.06	22.21	94.86	0.82
	BMI	−7.22	1.22	<0.01	−9.54	1.57	<0.01
	Adj R^2	0.14			0.15		
Model (2)							
Plasma glucose	(Intercept)	5.01	0.39	<0.01	4.96	0.53	<0.01
	Constant High	0.11	0.17	0.52	−0.04	0.17	0.82
	Decrease	−0.18	0.13	0.18	−0.31	0.25	0.22
	Increase	0.41	0.17	0.02	0.35	0.21	0.09
	Adj R^2	0.33			0.33		
Plasma insulin	(Intercept)	13.02	9.15	0.16	18.85	9.06	0.04
	Constant High	14	3.98	<0.01	7.67	2.95	0.01
	Decrease	0.57	3.09	0.85	−2.99	4.28	0.49
	Increase	9.93	3.96	0.01	11.04	3.52	<0.01
	Adj R^2	0.09			0.09		
HOMA2 IR	(Intercept)	1.64	1.14	0.15	2.4	1.16	0.04
	Constant High	1.72	0.49	<0.01	0.95	0.38	0.01
	Decrease	0.07	0.38	0.85	−0.41	0.55	0.46
	Increase	1.3	0.49	0.01	1.44	0.45	<0.01
	Adj R^2	0.1			0.1		
HOMA2 %β	(Intercept)	126.6	25.5	<0.01	151.01	31.41	<0.01
	Constant High	35.83	11.08	<0.01	27.22	10.23	0.01
	Decrease	4.12	8.61	0.63	−0.6	14.85	0.97
	Increase	26.19	11.04	0.02	20.31	12.22	0.1
	Adj R^2	0.09			0.06		
HOMA2 %S	(Intercept)	117.2	67.63	0.08	−50.31	100.33	0.62
	Constant High	−54.48	29.4	0.07	−59.64	32.67	0.07
	Decrease	0.91	22.84	0.97	89.26	47.43	0.06
	Increase	−53.66	29.27	0.07	−80.83	39.02	0.04
	Adj R^2	0.01			0.05		
Model (3)							
Plasma glucose	(Intercept)	4.98	0.38	<0.01	5.21	0.03	<0.01
	BMI*Constant High	−0.03	0.06	0.59	−0.12	0.09	0.15
	BMI*Decrease	0.02	0.03	0.61	−0.02	0.09	0.77
	BMI*Increase	0.11	0.04	0.01	−0.04	0.06	0.48
	Adj R^2	0.4			0.11		
Plasma insulin	(Intercept)	14.66	8.16	0.07	11.44	8.31	<0.01
	BMI*Constant High	3.02	1.33	0.02	0.67	0.54	0.59
	BMI*Decrease	−1.64	0.68	0.02	0.10	1.31	0.94
	BMI*Increase	0.54	0.92	0.56	−0.83	0.89	0.35
	Adj R^2	0.3			0.23		
HOMA2 IR	(Intercept)	1.83	1.01	0.07	1.49	0.06	0.2
	BMI*Constant High	0.35	0.16	0.03	0.06	0.16	0.71
	BMI*Decrease	−0.2	0.08	0.02	0.01	0.17	0.94
	BMI*Increase	0.09	0.11	0.44	−0.10	0.11	0.34
	Adj R^2	0.31			0.24		
HOMA2 %β	(Intercept)	129.08	23.44	<0.01	105.25	55.45	<0.01
	BMI*Constant High	5.75	3.81	0.13	0.10	4.59	0.98
	BMI*Decrease	−5	1.96	0.01	2.05	4.85	0.67
	BMI*Increase	−3.47	2.63	0.19	−3.30	3.31	0.31
	Adj R^2	0.26			0.16		

(*continued on next page*)

Table 3 (*continued*)

Outcome	Predictor	40s			60s		
		b	SE	p	b	SE	p
HOMA2 %S	(Intercept)	112.34	64.21	0.08	121.63	5.85	<0.01
	BMI*Constant High	3.54	10.44	0.73	9.83	14.18	0.49
	BMI*Decrease	6.06	5.38	0.26	−29.87	−1.99	0.05
	BMI*Increase	5.64	7.2	0.43	13.56	10.21	0.19
	Adj R^2	0.13			0.21		

Note: PA = Physical activity. Outcomes were plasma glucose, insulin, HOMA2-IR, HOMA2-%β and HOMA2-%S. Three models were fit: (1) the impact of BMI (at wave 4) on outcomes, (2) the impact of trajectory on outcomes, then (3) the interaction between BMI (at wave 4) and trajectory on outcomes. All models adjust for age, gender, hypertension, pre-clinical diabetes status (base group for comparison is normal fasting glucose, IFG = impaired fasting glucose), and physical activity.

body mass [24]. Our findings also somewhat reconcile these seemingly contradictory viewpoints.

We found similar elevations in beta cell function associated with constant high and increasing weight trajectories, compared with a constant normal trajectory. Animal models demonstrate that beta cell function is a consequence of an ongoing process of cell loss and renewal, and individuals with consistent weight experience consistent tension between obesity-associated adaptive increase and maladaptive decrease in beta cell mass and functioning [25]. This tension may be disrupted when oxidative stress, inflammation and hyperglycaemic toxicity associated with increasing body mass outstrips the pace of obesity-related adaptive beta cell mass increase. The interaction between BMI and beta cell function in the decrease trajectory for 40s but not 60s may be indicative of some recuperative function in younger adults, which allies with animal models which demonstrate that the capacity to recover lost beta cell mass diminishes with age [26]. There is considerable scope for further research to directly address the specific mechanisms underlying the proposed time-varying balance between weight-associated loss and increase in beta cell function.

Our novel attention to interaction between preceding trajectory and momentary BMI somewhat supported the proposition that insulin resistance associated with obesity may prevent additional weight gain [13,14]. Both the constant high and increase trajectories were similarly related to higher plasma insulin and insulin resistance, both sufficiently to qualify individuals in those groups as insulin resistant with a cutoff of HOMA2-IR >2 [27], yet only the interaction between BMI and the constant high trajectory was significantly associated with insulin function.

Although biological models would predict that weight loss in the context of obesity should be associated with decreased insulin secretion, some studies have indicated that obesity-related insulin hypersecretion continues after weight loss [15]. Our investigation of community-living adults followed over a decade (rather than, for example, individuals immediately following post-bariatric surgery) found no main effect difference between the weight loss and constant normal trajectories. Despite their weight loss over time, individuals in the weight loss trajectory tended to be obese at baseline and still had higher BMI (averaging on the border of overweight/obese) at final follow-up when compared with those in the constant normal weight trajectory (averaging on the border of normal/overweight) [28]. This not only suggests that obesity-related hypersecretion of insulin does diminish given sufficient time, but further emphasises the beneficial effects of weight loss even if momentary BMI remains high [12].

This study has some limitations and some significant strengths. Synthesis across cohort studies to date has been complicated by selection of particular sub-populations, and focus on differing time scales. Studies regarding weight loss typically having shorter durations (e.g. 2 years [12]) than studies focussing on weight gain (e.g. 10–20 years [10,11]). We have addressed this by examining a large community-living sample, and multiple trajectories of weight change measured in the same timeframe. Although generalizability may be limited due to selection effects in PATH and the current sub-sample, self-reported weight in the current study is commensurate with national measures [29].

The primary limitation was the use of BMI from self-report as a measure of body weight, rather than the body fat mass. Individuals typically under-report weight, but this does not threaten conclusions because of the focus on within-subject change. Although BMI is used extensively as a proxy for adiposity [30], it cannot provide information about the proportion of fat to muscle mass, which can influence the association between overall body weight and insulin metabolism [15]. Accordingly, further research could build on current findings by calculating weight trajectories from biomarkers such as leptin.

The objective of this study was to examine the relationship between trajectories of weight change over twelve years and blood glucose and insulin functioning in a sample of both diabetic and non-diabetic community-living middle aged and elderly adults, spanning the normal weight range. Results support the assertion that the trajectory of preceding weight change has a simultaneous, independent, and clinically meaningful effect on blood glucose metabolism beyond body weight measured at any given point in time.

Conflict of interest

None.

Acknowledgements

The authors are grateful to Kaarin Anstey, Anthony Jorm, Andrew MacKinnon, Helen Christensen, Bryan Rodgers, Simon Easteal, Peter Butterworth, Perminder Sachdev, Walter Abharathna, Marc Budge, and the PATH project interviewers. The PATH Through Life Study was funded by grants from the National Health and Medical Research Council [grant numbers 229936, 179839, 973302, 179805, 418039, 1002160, 157125, 350833, 1063907], Safework Australia, and the Department of Education, Employment and Workplace Relations. Nicolas Cherbuin's Research Fellowship is funded by the Australian Research Council [grant number 120100227]. Jonathan Shaw's Research Fellowship is funded by the National Health and Medical Research Council Fellowship [grant number 1079438].

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2017.12.003.

References

[1] Wannamethee SG, Shaper AG, Walker M. Overweight and obesity and weight change in middle aged men: impact on cardiovascular disease and diabetes. J Epidemiol Commun Health 2005;59(2):134–9.
[2] Lindström J, Tuomilehto J. The Diabetes Risk Score A practical tool to predict type 2 diabetes risk. Diabetes Care 2003;26(3):725–31.
[3] Bays HE, Chapman R, Grandy S. The relationship of body mass index to diabetes mellitus, hypertension and dyslipidaemia: comparison of data from two national surveys. Int J Clin Pract 2007;61(5):737–47.
[4] Golay A, Ybarra J. Link between obesity and type 2 diabetes. Best Pract Res Clin Endocrinol Metabol 2005;19(4):649–63.
[5] Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. Am J Epidemiol 1997;146(3):214–22.
[6] Camps SG, Verhoef SP, Westerterp KR. Physical activity and weight loss are independent predictors of improved insulin sensitivity following energy restriction. Obesity 2016;24(2):291–6.
[7] Horton ES, Silberman C, Davis KL, Berria R. Weight loss, glycemic control, and changes in cardiovascular biomarkers in patients with type 2 diabetes receiving incretin therapies or insulin in a large cohort database. Diabetes Care 2010;33(8):1759–65.
[8] Rosengren A, Wedel H, Wilhelmsen L. Body weight and weight gain during adult life in men in relation to coronary heart disease and mortality. Eur Heart J 1999;20(4):269–77.
[9] Huang Z, Willett WC, Manson JE, Rosner B, Stampfer MJ, Speizer FE, et al. Body weight, weight change, and risk for hypertension in women. Ann Intern Med 1998;128(2):81–8.
[10] Jernström H, Barratt-Conner E. Obesity, weight change, fasting insulin, proinsulin, C-peptide, and insulin-like growth factor-1 levels in women with and without breast cancer: the Rancho Bernardo study. J Womens Health Gend Based Med 1999;8(10):1265–72.
[11] Norman J, Bild D, Lewis C, Liu K, West DS. The impact of weight change on cardiovascular disease risk factors in young black and white adults: the CARDIA study. Int J Obes 2003;27(3):369–76.
[12] Sjöholm K, Pajunen P, Jacobson P, Karason K, Sjöström CD, Torgerson J, et al. Incidence and remission of type 2 diabetes in relation to degree of obesity at baseline and 2 year weight change: the Swedish Obese Subjects (SOS) study. Diabetologia 2015;58(7):1448–53.
[13] Swinburn BA, Nyomba BL, Saad MF, Zurlo F, Raz I, Knowler WC, et al. Insulin resistance associated with lower rates of weight gain in Pima Indians. J Clin Investig 1991;88(1):168.
[14] Eckel R. Insulin resistance: an adaptation for weight maintenance. Lancet 1992;340(8833):1452–3.
[15] Ferrannini E, Camastra S, Gastaldelli A, Sironi AM, Natali A, Muscelli E, et al. Beta-cell function in obesity effects of weight loss. Diabetes 2004;53(Suppl. 3):S26–33.
[16] Polonsky KS, Sturis J, Bell GI. Non-insulin-dependent diabetes mellitus—a genetically programmed failure of the beta cell to compensate for insulin resistance. N Engl J Med 1996;334(12):777–83.
[17] Anstey KJ, Christensen H, Butterworth P, Easteal S, Mackinnon A, Jacomb T, et al. Cohort profile: the PATH through life project. Int J Epidemiol 2012:dyr025.
[18] Carantoni M, Zuliani G, Munari M, d'Elia K, Palmieri E, Fellin R. Alzheimer disease and vascular dementia: relationships with fasting glucose and insulin levels. Dement Geriatr Cognit Disord 2000;11(3):176–80.
[19] Kukull WA, Larson EB, Teri L, Bowen J, McCormick W, Pfanschmidt M. The Mini-Mental State Examination score and the clinical diagnosis of dementia. J Clin Epidemiol 1994;47(9):1061–7.
[20] Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27(6):1487–95.
[21] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2005;28:S37.
[22] Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32(9; SUPP/1):S498–504.
[23] Dor Y, Brown J, Martinez OI, Melton DA. Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation. Nature 2004;429(6987):41–6.
[24] Donath M, Halban PA. Decreased beta-cell mass in diabetes: significance, mechanisms and therapeutic implications. Diabetologia 2004;47(3):581–9.
[25] Flier SN, Kulkarni RN, Kahn CR. Evidence for a circulating islet cell growth factor in insulin-resistant states. Proc Natl Acad Sci 2001;98(13):7475–80.
[26] Tschen S-I, Dhawan S, Gurlo T, Bhushan A. Age-dependent decline in β-cell proliferation restricts the capacity of β-cell regeneration in mice. Diabetes 2009;58(6):1312–20.
[27] Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord 2013;13(1):1.
[28] Organization WH. Obesity: preventing and managing the global epidemic. World Health Organization; 2000.
[29] Australian Bureau of Statistics. National health survey: summary of results, 2001. 2002.
[30] Bouchard C. BMI, fat mass, abdominal adiposity and visceral fat: where is the 'beef'? Int J Obes 2007;31(10):1552–3.