What scope is there for averting the adverse health effects of obesity? Investigating the role of physical activity.

Final Report

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Preface – what the study adds to knowledge

Currently, with high prevalence levels of obesity, a key public health priority is to identify modifiable risk factors that lessen the impact of obesity on the population burden of related health consequences. Our aim was to inform public health strategies, by establishing whether health hazards of obesity are modifiable by physical activity (or sedentary behaviour) in a contemporary adult population (1958 British birth cohort) exposed to the obesity epidemic from their early twenties to mid-life. Approximately 25% of the population were obese by 45y, and of this group, most (59%) had onset in mid-adulthood, whilst 7.6% were obese from childhood; a further 41% were identified as overweight. At 33y, approximately 11% were identified as obese.

Our observational study demonstrated the expected (detrimental) associations between obesity and biomarkers for CVD and diabetes in mid-adulthood (45y) including systolic and diastolic blood pressure (SBP and DBP), blood lipids (triglycerides, LDL and HDL cholesterol) and glucose metabolism (HbA1c). Notably, in more in depth work for HbA1c, childhood obesity onset was associated with the greatest risk of type 2 diabetes (almost 24-fold risk compared to the never obese) and there was a high risk also for the more prevalent group with childhood overweight onset. These elevated risks for diabetes were mainly due to the higher mean BMIs and waist circumference at 45y of those with childhood or young adulthood obesity (or overweight) onset. These findings highlight the benefits of delaying onset of overweight and obesity and argue for interventions to support obesity prevention in childhood.

Higher sedentary behaviour (sitting at work and TV-viewing) and lower physical activity were associated with several CVD/diabetes biomarkers. Increased sitting at work and TV-viewing both showed adverse associations with blood lipids (triglycerides and HDL-cholesterol) independent of activity levels. Associations were stronger for TV-viewing, which was associated with additional CVD biomarkers (SBP, DBP and HbA1c). These findings add to evidence from other recent studies suggesting a role for sedentary behaviour independent of activity. Yet, our study raises questions on its importance for some biomarkers given inconsistencies for indicators of sedentary behaviour. Physical activity was associated with some biomarkers. More detailed analyses of BP and lipids add to the scant evidence from longitudinal studies by showing associations with lack of activity many years before biomarker assessment subsequently at 45y. Moreover, cumulative activity (23 and 45y) associations were observed for BP, although less so for lipids, suggesting that for some biomarkers there are benefits of becoming active and sustaining activity over many years of life.

For some CVD biomarkers, e.g. BP, associations of activity (or sedentary behaviour) were not independent of BMI. This implies that the influence of (in)activity may operate in part via adiposity. Support for effect modification was observed, at least for some biomarkers. For HbA1c, associations with activity and TV-viewing were stronger for the obese group. Specifically, the reduction in HbA1c level with increasing activity was greater among obese than the non-obese and there was a greater detrimental association of high TV-viewing among the obese. Such interactive effects argue for changes in these behaviours to lessen the impact of obesity on risk of type 2 diabetes. Our observational findings based on longitudinal data therefore provide some support for the argument that health hazards of obesity might be minimised with reduced sedentary behaviour and increased physical activity.

Executive Summary

Background: A substantial proportion of the British population is now at risk of obesity-related ill-health: 22% of men and 24% of women were identified as obese in the *Health Survey for England* in 2009. Policies to halt the rising trend in obesity are important, but action is needed simultaneously for the generations already affected. A key public health priority is therefore to minimise obesity-related health consequences. In this context, potentially important modifiable factors include physical activity and sedentary lifestyles, which have been related to cardiovascular disease (CVD) and type 2 diabetes.

Some observational studies suggest that obese groups may have a greater health benefit of being physically active or less sedentary than the non-obese, particularly for type 2 diabetes risk, but to date the evidence base is limited. Improved understanding is needed of health benefits that might accrue from activity or reduced sedentary behaviour across different life-stages when changes in lifestyles or adiposity occur. Whether health benefit is achieved via weight control is of further interest. From a public health perspective it is important to identify the benefit to obese groups of increased activity or reduced sedentary behaviour.

Aims: Our project seeks to inform strategies to minimise the health consequences of obesity. We used a nationwide sample, studied from birth to 45y (1958 British birth cohort) to investigate the interplay between physical activity/sedentary behaviour, obesity and biomarkers for CVD and type 2 diabetes. Our objective was to identify whether health consequences of obesity are modifiable by physical (in)activity; specifically, to establish whether:

(i) effects of obesity on biomarkers for CVD and diabetes are modifiable by (in)activity;

(ii) both level and change in (in)activity in early adult life affect the association between obesity and CVD risk (timing of (in)activity was a focus, to establish whether "it is never too late" to alter health outcomes).

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Study population: Information for the 1958 cohort was collected prospectively for all born in England, Wales and Scotland (~17,000), followed to age 45y when a biomedical survey was undertaken (n=9337). Body mass index (BMI) was obtained from heights and weights recorded in childhood (7,11,16y) and adulthood (23,33,42,45y); obesity was defined using standard cut-offs. Activity was recorded from questionnaire in adulthood: leisure-time activity frequency (23,33,42,45y) and work activity (45y); for sedentary behaviour, TV-viewing (23,45y) and sitting at work (45y).

CVD biomarkers at 45y include: blood pressure (three measures with the participant rested for 5mins; a large cuff was used when mid-upper arm circumference $\geq$32cm); blood lipids (triglycerides, total, low and high density lipoprotein (LDL and HDL) cholesterol) and glycosylated haemoglobin (HbA1c) from non-fasted venous blood samples; medications, e.g. for blood pressure or diabetes. Data were available on potential confounding factors spanning child to adulthood.

Prevalence of obesity, activity and sedentary behaviour: Approximately 25% of the population were obese by 45y, most (59%) of whom had onset in mid-adulthood, whilst 7.6% were obese from childhood. A further 41% of the population were identified as overweight at 45y. At 33y, approximately 11% were identified as obese. At 45yrs, most of the population participated in moderate-vigorous leisure activity, 38% at a frequency of ≥6 times/wk. More than one in 5 reported TV-viewing for >3h/day, whilst ~43% reported sitting at work for >3h/day.

Associations between obesity and CVD biomarkers: In both men and women, obesity at 33y was associated with several CVD biomarkers measured twelve years later at 45y, namely, higher systolic and diastolic blood pressure (SBP and DBP), HbA1c and

triglycerides and with lower HDL cholesterol. In women only, obesity at 33y was also associated with higher LDL cholesterol. Estimated elevated levels associated with obesity (33y) ranged from ~4% to ~19% in men, for SBP and triglycerides respectively, and from ~4% to ~27% in women for LDL-cholesterol and triglycerides. The estimates were obtained from analyses that allowed for other factors, such as diet, smoking and education level.

Studying the association between BMI and risk of type 2 diabetes in more detail, we examined whether there are effects of (i) sensitive periods of BMI gain, or (ii) long duration of overweight and obesity. The prevalence of risk of type 2 diabetes at 45y was 2% (including HbA1c≥7%). We found that BMI gains in child and adulthood were associated with higher HbA1c: for every standard deviation (SD) of 5y BMI increase, from ages 0-7y, there was a 75% (OR=1.75, 95%CI=1.42-2.16) elevated risk of type 2 diabetes, increasing to a 4.7-fold (3.12-7.00) risk for the interval, 23-33y. Associations for BMI gain in adulthood were related to attained BMI, but associations for the longer period birth to 45y were independent of BMI at 45y. Thus, BMI gain in the first decade of life may be important for adult glucose metabolism out-with any influence of gain on adult adiposity. BMI gain throughout adulthood also contributed to glucose levels, but via an influence on attained BMI at 45y.

Duration of obesity was associated with HbA1c: compared to the never obese, those with childhood onset had a 23.9-fold risk (13.5-42.1) of HbA1c≥7%; odds ratios were 16.0 (10.6-24.2) and 2.99 (1.77-5.03) respectively for young and mid-adulthood onset. Similar trends were found in mean HbA1c levels and for onset of overweight. Those with the earliest age of onset had higher BMI and waist circumference at 45y which markedly explained the associations for onset age and HbA1c. These findings are important given recent increasing trends in overweight and obesity in many countries. Young children today are overweight earlier in their lives than previous generations, including our cohort.

For a minority of individuals overweight in childhood but not in adulthood, HbA1c levels were not elevated. This finding suggests that detrimental effects of child overweight might be averted if BMI gain with increasing age can be controlled. Those who were obese in childhood and not thereafter had a five-fold risk of HbA1c≥7% after adjustment for 45y adiposity. This suggests a long-lasting risk for impaired glucose metabolism in association with childhood obesity irrespective of adult obesity, arguing for primary prevention in childhood. Further studies are warranted to confirm or refute this finding.

Our study suggests that there are benefits of delaying onset of overweight and obesity, in that risks of elevated HbA1c were lower for 45 year-olds becoming overweight or obese in the previous 12y than for earlier onset. Arguably, interventions to prevent obesity are best targeted in childhood. Because excessive BMI gain was associated with elevated HbA1c (albeit via attained BMI) even in those of normal weight, suggests that weight gain across the full distribution might be a worthwhile focus for type 2 diabetes prevention.

Activity/sedentary behaviour and CVD biomarkers:
(i) Sedentary behaviour (TV-viewing and sitting at work) and CVD biomarkers: cross-sectional study.
We sought to establish whether (1) associations for (i) TV-viewing and (ii) sitting at work with CVD biomarkers at 45y are consistent in direction and magnitude, and (2) TV-viewing and sitting at work are independent risk factors for CVD biomarkers. Given uncertainty about what these indicators represent, we also examined patterns of association with covariates.

Clustering of covariates differed for the two indicators: high (>3h/day) TV-viewing was associated with manual class, lower education, low fruit and high chips consumption,

smoking, obesity and infrequent activity; trends for sitting at work were in the opposite direction.

TV-viewing was associated with an adverse CVD profile: for women total and LDL cholesterol, triglycerides, systolic and diastolic blood pressure (SBP and DBP) were higher by 0.8% to 4.5% and HDL was lower by 2.0% per category increase of TV-viewing (i.e. 0-1, 1-2, 2-3 and >3 h/day); for men, triglycerides, SBP and DBP were higher by 0.4% to 4.5% and HDL was lower by 2.3% per increase in TV-viewing category. No association was seen for HbA1c and most but not all associations were mediated, at least in part, by BMI. In comparison, associations for sitting at work tended to be weaker.

Our findings support an association between sedentary behaviour and CVD biomarkers, particularly for lipids. Yet, two measures of sedentary behaviour vary in their association with CVD biomarkers, possibly because the role of sedentary behaviour varies by domain (with differences in energy expenditure for each behaviour). Alternatively, the clustering of covariates suggests that the two indicators reflect a different constellation of factors, past and present, associated with CVD biomarkers.

(ii) Physical activity and sedentary behaviour over different ages in adulthood: longitudinal study of adult blood pressure and lipids.
For BP, there was little evidence of a trend across frequency of activity, rather there was a threshold associated with (dis)benefit for active vs inactive (e.g. not active in last month at 23y or <2-3 times/month at 33y). Activity 23 to 45y was associated with lower SBP and DBP by ~1-2mmHg and reduced risk of hypertension by ~23% depending on activity assessment age. Associations tended to be linear for lipids, e.g. HDL increased by 0.006mmol/L and triglycerides decreased by 1.4% for each day/week of activity participation at 42y. (Few associations were found for total or LDL-cholesterol). These results suggest that benefits for BP may be associated with a minimum activity frequency, whereas improvements in HDL-cholesterol and triglyceride levels are likely to be gained incrementally with activity level. Many, but not all, associations attenuated with adjustment for BMI, suggesting a salient mediating role for adiposity.

We found some associations for activity participation decades before BP and lipid measurement at 45y: e.g. 23y activity was associated with lower risk of hypertension and in women, with higher HDL-cholesterol. For BP, there was some suggestion of cumulative associations: early adult activity was associated with hypertension independently of recent activity, which was also associated with BP. In men for example, prevalence of hypertension was highest in those who were inactive at both 23 and 45y (39%) and lowest in those who were active at both ages (31.4%). These findings are consistent with a benefit to BP of becoming active and cumulative benefit of sustaining active lifestyles over many years. Similarly, TV-viewing at 23 and 45y were both associated independently with SBP, DBP and hypertension for men, suggesting a cumulative association: e.g. men with low TV-viewing at 23y (<1-2 times/week) who maintained a low level at 45y (<1h/day) had an estimated prevalence of hypertension of 31.2%, whereas, for men with high TV-viewing at 23y (>5 times/week) and 45y (>3h/day) the estimate was 37.3%. For lipids, support for cumulative benefits of activity was more limited and no cumulative association for TV-viewing was found.

Combined and interacting associations between physical activity (or sedentary behaviour), obesity and biomarkers for CVD and type 2 diabetes
To clarify the extent to which effects of obesity on CVD biomarkers may be modified by activity and sedentary behaviour (indexed by TV-viewing) we examined the association between obesity in early adulthood (33y) with biomarkers at follow-up 12y years later, when activity and TV-viewing were also assessed. We used measures at these time-points to follow, to the extent possible in an observational study, the sequence of an activity/ sedentary behaviour intervention targeted at obese and non-obese groups. We assessed:

i) Independence of associations: For obesity, associations were largely independent of activity, TV-viewing and other covariates, with biomarker levels estimated to be ~4 to ~27% higher for the obese group. TV-viewing associations attenuated after adjustment for lifestyle and socio-economic factors, but some biomarkers were associated independently of BMI and activity, with levels elevated by ~1 to ~5% for those watching >3h/day. Weaker associations for physical activity were largely attenuated after adjustment for covariates.

ii) Moderating associations (interactions): We found some support for moderating associations of activity and TV-viewing on the association of obesity with HbA1c. In obese men, HbA1c levels at 45y were lowered as frequency of moderate-vigorous activity increased, whereas the association was weak in non-obese men. For both sexes, the TV-viewing and HbA1c association was stronger for the obese, such that mean HbA1c levels increased with greater hours of TV-viewing; associations in the non-obese were weak. In general, these findings of moderating associations were confirmed in additional analyses of obesity at later ages (42y and 45y). Preliminary results suggest that there may be a similar moderating association of activity on the obesity/blood pressure relationship, with a stronger protective association of activity for the obese. Associations were borderline and further analyses are planned to confirm these results. Little support was found for moderating associations on the obesity and blood lipids associations.

Conclusions: Our study highlights the importance of obesity for several biomarkers for CVD and type 2 diabetes in a general population of middle-aged adults. Whilst based on observational data, with the limitations that this imposes, our study has notable strengths owing to availability of longitudinal data over decades of follow-up, in a generation exposed to the obesity epidemic for many years (i.e. from their early twenties).

Several implications of our research for public health prevention strategies include: (1) risks of elevated HbA1c were lower for 45 year-olds becoming overweight or obese in the previous 12y than for earlier onset, highlighting the need to prevent early life onset of overweight and obesity; (2) blood lipids were adversely associated with sedentary behaviour, although most notably with TV-viewing. Given that that TV-viewing was associated with other biomarkers and also clusters with CVD-related lifestyles and socio-demographic factors, it may be an important modifiable risk factor to target; (3) the association of lack of activity in early adulthood with BP and blood lipids subsequently at 45y, in some instances, with cumulative (23 and 45y) associations, is consistent with health benefits of becoming active and sustaining activity over many years of life; and (4) the stronger associations for HbA1c among obese than non-obese groups, protective for activity and detrimental for TV-viewing, argues for changes in these behaviours to lessen the impact of obesity on risk of type 2 diabetes.

Implications for future public health research include the need to advance our knowledge of the role of sedentary behaviour on health outcome and of measurement issues. Our project has focussed only on physical activity and sedentary behaviour as potential modifying influences on the association between obesity and CVD/diabetes biomarkers. Further research to improve understanding of how to lessen the impact of obesity on associated disease risk is warranted.

Detailed summary of work

Overview

This report gives a brief background of work on cardiovascular disease (CVD) and type 2 diabetes risk and the role of obesity, physical activity and sedentary behaviour and sets out the evidence gaps that the project aims to address. It then describes the analysis undertaken on:

i) obesity and CVD biomarkers in mid-adulthood;
ii) activity or sedentary behaviour and CVD biomarkers
iii) interactions between obesity and activity (or sedentary behaviour) on CVD biomarkers.

Finally it draws conclusions, focusing on considering the relevance of the study findings for public health and policy.

Background

A substantial proportion of the British population is now at risk of obesity-related ill-health: 22% of men and 24% of women were identified as obese in the *Health Survey for England* in 2009. Policies to halt the rising trend in obesity are important, but action is needed simultaneously for the generations already affected. A key public health priority is therefore to minimise obesity-related health consequences. In this context, potentially important modifiable factors to consider include physical activity and sedentary lifestyles, which have been identified as related to CVD, type 2 diabetes and some cancers.

Recent research suggests that there is a need to consider the joint effects on risk of CVD and type 2 diabetes of both physical activity (or sedentary behaviour) and obesity in order to clarify the interplay between these factors. There is some evidence from observational studies to suggest that obese groups may have a greater health benefit of being physically active/less sedentary than the non-obese. In a Finnish study, the impact of leisure time activity (active vs sedentary) on the risk of ischemic heart disease death tended to be stronger in men whose BMI was ≥27 kg/m^2 (Salonen et al, 1988). Whilst, consistently for five studies included in a recent review, obese groups who were physically inactive had an increased risk of type 2 diabetes that was greater than the additional effect of each factor separately (Qin et al, 2010). Not all studies show this greater benefit for CVD or diabetes of activity amongst obese groups (Winjdaele et al, 2010; Siegel et al, 2009), but to date evidence has been limited for some CVD-related outcomes and for sedentary behaviour (Winjdaele et al, 2010; Martinez-Gomez et al, 2010). Moreover, evidence from longitudinal studies remains scant despite some exceptions (Meyer et al, 2002; Weinstein et al, 2004, 2008; Siegel et al, 2009; Rana et al, 2007; Hu et al, 2004; Kriska et al, 2003; Hu et al, 1999; Helmrich et al, 1991).

The benefits of greater activity or reduced sedentary behaviour on health are important to document across different life-stages during which changes in lifestyles and adiposity can occur. Whether health benefit is achieved via weight control and subsequent adiposity level is of further interest. Importantly from a public health perspective is to identify the benefit to obese groups of increased activity or reduced sedentary behaviour. If increased activity or reduced sedentary behaviour are found to be particularly beneficial to obese groups these lifestyle changes would be important for minimising the associated health consequences of obesity, and thereby, of key relevance for public health policy. Such interactive effects imply, as argued elsewhere in a study of risk of type 2 diabetes, that "prevention of either obesity or physical inactivity, not only reduces the risk of diabetes by taking away the independent effect of this factor but also by preventing the cases that are caused by the interaction between both factors" (Qin et al, 2010).

Given the need for strategies to minimise the associated health consequences of obesity, in addition to those aimed at primary prevention of obesity, our project aims to inform such strategies by seeking to identify whether health consequences of obesity are modifiable by physical activity. For example, is an overweight adult who takes up regular physical activity at lower risk of obesity-related disease than one who persists with less healthy activity patterns? The timing of the modifying influence of activity will be a focus, to establish whether "it is never too late" to alter health outcomes.

We use a nationwide sample, studied from birth to 45y (1958 British birth cohort) to investigate the interplay between physical activity/sedentary behaviour, obesity and biomarkers for CVD/diabetes. The cohort provides rich observational data to control for potential confounding factors (e.g. diet) spanning from childhood to adulthood.

Aims

Our study objective was to identify whether health consequences of obesity are modifiable by physical (in)activity (and whether any modifying effect of activity varies by social position).

Specifically, our objectives are to establish whether:

- effects of obesity on biomarkers for CVD and diabetes are modifiable by physical activity. We would, for example, investigate whether individuals who are obese, but who are regularly physically active in adulthood are at lower risk of obesity-related disease than individuals with less active lifestyles.

- both level and change in physical activity in early adult life affect the association between obesity and biomarkers for CVD. The timing of activity will be a focus, to establish whether "it is never too late" to alter health outcomes.

Methods

Study sample: The research is based on a large nationwide population with information collected prospectively, the 1958 British birth cohort, covering all born in England, Wales and Scotland, during one week in 1958. Participants are survivors from an original sample of over 17,000 births, followed-up by parental interview and examination throughout childhood and by interview in adulthood (Power and Elliott, 2006). During childhood, individuals were traced through schools and immigrants born in the reference week were added to the sample. The first biomedical assessment in adulthood was conducted at age 45y (n=9337). Ethical approval for the biomedical survey was obtained from South-East Multi-Centre Research Ethics Committee. Participants gave consent for specific measures (e.g weight and height) and for use of their blood samples in medical research studies of the causes, diagnosis, treatment and outcome of diseases.

Details of measures and collection methods and data analytic strategy are provided in Annex 1; here below we include brief details.

Measures: Body mass index (BMI) was obtained from heights and weights recorded in childhood (7,11,16y) and adulthood (23,33,42,45y); obesity was defined using standard cut-offs. Waist circumference measurements were obtained at 45y. Activity was recorded from questionnaire in adulthood: leisure-time activity frequency (23,33,42,45y) and work activity (45y); for sedentary behaviour, TV-viewing (23,45y) and sitting at work (45y). We identified individuals undertaking moderate or vigorous leisure activity at 45y in five categories: none in the last year, once a month or less, <3 times/wk, 3-5 times/wk and ≥6 times/wk.

CVD biomarkers obtained at 45y include: blood pressure (systolic (SBP), diastolic (DBP) and hypertension); blood lipids (total cholesterol, LDL and HDL cholesterol and triglycerides) and glycosylated haemoglobin (HbA1c) from non-fasted venous blood samples; medications, e.g. for blood pressure or diabetes. Risk of type 2 diabetes was identified from medication data, self-report and HbA1c≥7. Information on genetic factors was also obtained from the 45y blood sample.

Potential confounding factors included socio-demographic (e.g. social class and education level) and other lifestyle factors (e.g. diet, smoking and alcohol consumption) at different ages.

Analyses: Most CVD biomarkers were modelled as continuous outcomes, transformed where necessary, for each biomarker separately, with examination of whether associations were linear. Dichotomous outcomes were used in some instances (e.g. diabetes risk). We examined:

- the association between obesity and CVD biomarkers;
- the association between activity or sedentary behaviour and CVD biomarkers;
- whether there is an interaction between obesity and activity (or sedentary behaviour) on CVD biomarkers.

Several confounding and mediating factors were taken into account, varying as appropriate for biomarker outcome and the specific analysis undertaken. Footnotes for tables and figures specify the factors included in analyses and brief details of the general approach to potential confounding factors are given in the data analysis section of ANNEX 1.

Study limitations: As our study is based on observational data it has several limitations that should be acknowledged in interpreting the findings. These limitations include, for example, sample attrition and the potential for associated bias, differences across age of exposure measures and confounding factors. For each part of the work we assessed potential weaknesses and carefully considered different approaches, repeating analyses where possible to ensure that our findings were robust (e.g. in sensitivity analyses).

To some extent it was possible to take account of study limitations, e.g. with weighting and imputation methods for missing data and attrition. However, despite these efforts, some limitations remain. In particular, physical activity and sedentary behaviour were ascertained via questionnaire. Whilst such measures may be informative, the precision of exposures is likely to be affected by measurement error. As with alternative designs, not all study short-comings can be addressed, hence our findings should be interpreted as providing suggestive evidence on associations of interest.

In the data analysis section of ANNEX 1 we illustrate some of the approaches taken to minimise study limitations (and further details are provided in publications, as listed in the 'Outputs' section of the report).

Key findings

Prevalence of obesity: Approximately 25% of the population were obese by 45y (Table 1), and of this group, most (59%) had onset in mid-adulthood, whilst 7.6% were obese from childhood. A further 41% of the population were identified as overweight at 45y. At 33y, approximately 11% were identified as obese.

Table 1: Characteristics of 9337 participants in the 45y biomedical survey

		Total	**Men**	**Women**
	N‡	n(%) or mean (sd)	n (%) or mean (sd)	n (%) or mean (sd)
Obesity at 33 y	8189			
No		7346 (89.7)	3599 (90.2)	3747 (89.3)
Yes		843 (10.3)	393 (9.8)	450 (10.7)
Obesity at 45y	9348			
No		7054 (75.5)	3471 (74.6)	3583 (76.3)
Yes		2294 (24.5)	1180 (25.4)	1114 (23.7)
TV-viewing at 45y (h/d)	9125			
<3		7016 (76.9)	3452 (76.2)	3564 (77.6)
>=3		2109 (23.1)	1079 (23.8)	1030 (22.4)
Moderate vigorous leisure activity frequency at 45y	9178			
None		138 (1.50)	48 (1.05)	90 (1.95)
Infrequent		671 (7.31)	268 (5.88)	403 (8.72)
<3 times/wk		2249 (24.50)	1105 (24.26)	1144 (24.75)
3-5 times/wk		2615 (28.49)	1308 (28.72)	1307 (28.27)
≥6 times/wk		3505 (38.19)	1826 (40.09)	1679 (36.32)
CVD biomarkers at 45y				
Total cholesterol (mmol/L)	7824	5.9 (1.1)	6.1 (1.1)	5.7 (1.0)
LDL-cholesterol (mmol/L)	7380	3.4 (0.9)	3.6 (0.9)	3.3 (0.9)
HDL-cholesterol (mmol/L)	7808	1.6 (0.4)	1.4 (0.3)	1.7 (0.4)
Triglycerides (mmol/L)*	7799	1.6 (1.1, 2.5)	2.1 (1.4, 3.0)	1.3 (0.9, 1.9)
Diastolic blood pressure (mmHg)	9297	78.8 (10.8)	82.0 (10.4)	75.6 (10.2)
Systolic blood pressure (mmHg)	9297	126.6 (16.5)	132.9 (15.0)	120.3 (15.5)
HbA1c (%)*	7867	5.2 (5.0, 5.4)	5.2 (5.0, 5.5)	5.1 (4.9, 5.3)

‡ Total N varies due to variation in the amount of missing data
* median and inter-quartile range

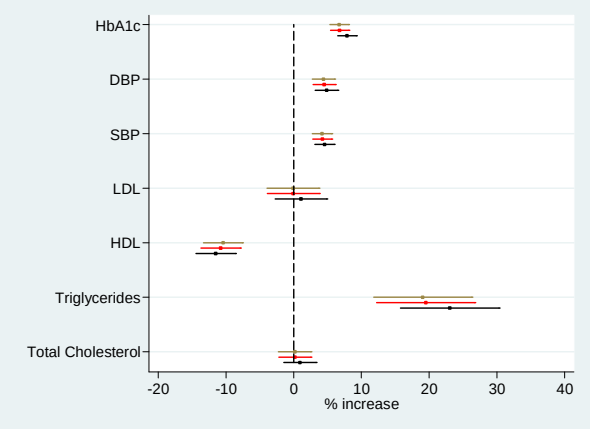
Obesity and biomarkers for CVD and type 2 diabetes *outputs 1,2*

A necessary pre-requisite for understanding any modifying effects of activity or sedentary behaviour was to determine the associations between obesity and CVD biomarkers in our study population.

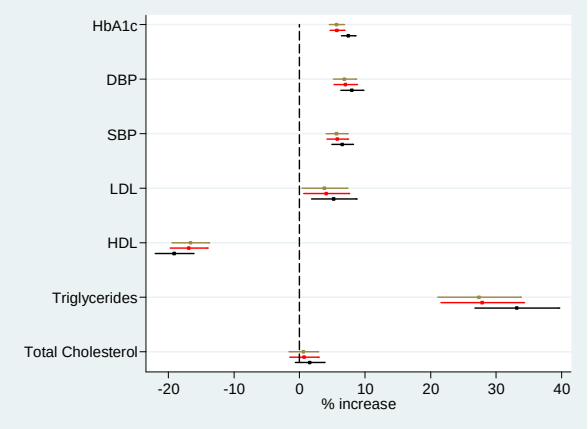
Figure 1 shows that, in both sexes, obesity at 33y was associated with higher SBP, DBP, HbA1c and triglycerides and with lower HDL cholesterol at 45y, and in women only, with higher LDL cholesterol.

Figure 1: Obesity at 33y and CVD/diabetes biomarkers at 45y

a) Men



b) Women



Corrected for medication for BP, lipids or T2 diabetes.

Black= Crude associations
Red = adjusted for smoking, socio-economic position (SEP), education , limiting daily activity longstanding illness, fruit, chips and alcohol consumption all at 33y + birth-weight.
Additional adjustment for women: HRT, menopausal status and OC use all at 45y.
Additional adjustment for all outcomes except lipids (HDL and LDL cholesterol and triglycerides): total and HDL cholesterol
Additional adjustment for all outcomes except SBP & DBP: Hypertension: yes/no
Brown = Red model + physcial activity at 45y + TV at 45y

Glucose metabolism *output 2*

In more detailed investigation of adult glucose metabolism /type 2 diabetes risk in mid-adulthood we examined whether there are effects of:

(i) sensitive periods of BMI gain, or
(ii) long duration of overweight and obesity.

In 7855 participants with information on BMI at several time-points from child to adulthood and glycosylated haemoglobin (HbA1c) at 45y, there was a prevalence of type 2 diabetes or HbA1c≥7 of 2%.

BMI gains in child and adulthood were associated with higher HbA1c: for every SD of 5y BMI increase, from 0-7y, there was a 75% (OR=1.75, 95%CI=1.42-2.16) increased risk of HbA1c≥7%, increasing to a 4.7-fold (3.12-7.00) risk for the interval, 23-33y. Associations for BMI

gain in adulthood were related to attained BMI, but were independent for the longer period birth (or 7y) to 45y (Table 2).

Duration of obesity was also associated with HbA1c: compared to the never obese, those with childhood onset had a 23.9-fold risk (13.5-42.1) of HbA1c≥7%; odds ratios were 16.0 (10.6-24.2) and 2.99 (1.77-5.03) respectively for young and mid-adulthood onset (Table 3).

Similar trends by onset age were found in mean HbA1c levels and for onset of overweight. Those with the earliest age of onset had higher BMI and waist circumference at 45y which markedly explained the associations for onset age and HbA1c.

Table 2: Odds ratios for elevated HbA1c≥7 at 45y and difference in HbA1c (unit %) (i) per SD of 5-year BMI change during different life periods adjusted for baseline BMI, and (ii) per SD of BMI at each age adjusted for BMI at 45y (n=7855)*

	HbA1c≥7†	HbA1c§
	OR (95% CI)	Difference (95% CI)
BMI change between ages (y)	Adjusted for baseline BMI	
Birth to 7	1.75 (1.42, 2.16)	0.029 (0.008, 0.050)
7-11	1.66 (1.45, 1.90)	0.040 (0.020, 0.061)
11-16	2.06 (1.69, 2.51)	0.042 (0.013, 0.070)
16-23	2.99 (2.31, 3.87)	0.095 (0.063, 0.127)
23-33	4.67 (3.12, 7.00)	0.205 (0.142, 0.268)
33-45	1.24 (0.74, 2.07)	0.155 (0.092, 0.218)
BMI (SD score) at (years)	Adjusted for BMI at 45y	
0	0.90 (0.75, 1.07)	-0.024 (-0.037, -0.011)
7	1.02 (0.86, 1.21)	-0.015 (-0.030, 0.000)
11	1.21 (1.03, 1.43)	-0.005 (-0.023, 0.013)
16	1.44 (1.23, 1.68)	-0.002 (-0.025, 0.021)
23	1.83 (1.52, 2.21)	0.004 (-0.019, 0.027)
33	2.56 (2.08, 3.14)	0.048 (0.012, 0.085)

* Results estimated using multiple imputation
† includes diagnosed type 2 diabetes.
§ Models control for type 2 diabetes treatment
All models adjusted for gender, social class in childhood and at 42y, family history of diabetes, ethnicity

Table 3: Association between age of onset of overweight or obesity and adult HbA1c: odds ratios for elevated HbA1c≥7 and regression coefficients for change in HbA1c (unit %)

Duration/age of onset	N (%)‡	BMI 45y (kg/m^2)	Waist circumference (cm)	HbA1c≥7* OR (95%CI)		HbA1c coefficient (95%CI)§	
(n=7855)†		mean(95%CI)‡	mean(95%CI)‡	Unadjusted	Adjusted$	Unadjusted	Adjusted$
Obesity							
Never	5820 (74.1)	25.1 (25.0 ,25.2)	86.9 (86.6 ,87.2)	-	-	-	-
Childhood only	62 (0.8)	26.3 (25.5 ,27.0)	90.6 (87.9 ,93.4)	7.01 (1.89, 25.89)	4.95 (1.30, 18.93)	0.034 (-0.147, 0.214)	0.012 (-0.158, 0.181)
Onset in mid-adulthood	1171 (14.9)	32.5 (32.3 ,32.7)	103.5 (102.8 ,104.1)	2.99 (1.77, 5.03)	1.13 (0.61, 2.08)	0.151 (0.112, 0.189)	0.026 (-0.026, 0.078)
Onset in young adulthood	652 (8.3)	35.2 (35.0 ,35.5)	109.2 (108.3 ,110.0)	16.04 (10.63, 24.17)	3.96 (2.10, 7.43)	0.280 (0.211, 0.349)	0.115 (0.032, 0.199)
Onset in childhood	151 (1.9)	37.8 (37.2 ,38.4)	113.2 (111.4 ,115.1)	23.86 (13.52, 42.14) #	4.38 (1.86, 10.31) #	0.363 (0.173, 0.554) #	0.170 (-0.009, 0.348) #
Overweight (including obesity)							
Never	2366 (30.1)	22.6 (22.5 ,22.7)	80.0 (79.5 ,80.4)	-	-	-	-
Childhood only	163 (2.1)	22.6 (22.1 ,23.2)	78.1 (76.4 ,79.7)	-	-	-0.040 (-0.100, 0.021)	-0.035 (-0.094, 0.023)
Onset in mid-adulthood	1729 (22.0)	27.2 (27.1 ,27.4)	92.2 (91.7 ,92.6)	1.88 (0.66, 5.33)	0.77 (0.27, 2.19)	0.044 (0.022, 0.066)	-0.083 (-0.117, -0.050)
Onset in young adulthood	2396 (30.5)	29.9 (29.8 ,30.1)	99.2 (98.7 ,99.6)	8.63 (3.85, 19.32)	1.87 (0.79, 4.45)	0.112 (0.083, 0.141)	-0.088 (-0.133, -0.044)
Onset in childhood	1201 (15.3)	32.1 (31.9 ,32.3)	101.4 (100.8 ,102.1)	21.63 (9.77, 47.85) #	3.25 (1.30, 8.14) #	0.183 (0.134, 0.231) #	-0.059 (-0.116, -0.001) #

‡averaged across imputed datasets
*Type 2 diabetes or HbA1c≥7.
§Models control for type 2 diabetes treatment.
†Age at onset of obesity/overweight defined as: never (BMI < WHO cut-off at all ages); childhood only (BMI ≥ cut-off at 7, 11 or 16 years but not at 23, 33 & 45); onset in childhood or adolescence (BMI ≥ cut-off at 7, 11 or 16 plus 23, 33 or 45); onset in young adulthood (BMI ≥ cut-off at 23 or 33, but not in childhood); onset in mid-adulthood (BMI ≥ cut-off at 45 only).
$ gender, total cholesterol, HDL-cholesterol, family history of diabetes, menopausal status, smoking at 42y, alcohol consumption at 42y, social class in childhood, social class at 45y, qualifications by 42y.
# Linear trend from never to onset in mid-adulthood $p<0.05$ (tested including and excluding category of childhood only)

Three main findings were identified from this study:
(summarised from Tables 2 and 3 for HbA1c levels and HbA1c≥7%; supplementary tables in output 2 for HbA1c≥6%)

1. Excessive BMI gain at all life-stages was associated with elevated HbA1c levels, cumulatively across the lifespan. When concurrent (45y) BMI is taken into account, associations for adult BMI gain appeared to be largely due to their effect on attained BMI, whereas, BMI gain from the first decade of life remained associated with mean HbA1c levels and HbA1c≥6%, although not HbA1c≥7%. Our results suggest therefore that BMI gain in the first decade may be important out-with any influence of gain on adult adiposity.

2. Adults with overweight or obesity onset in childhood or young adulthood had the highest mean BMIs and waist circumference at 45y, and greatest risk of elevated HbA1c. Childhood obesity onset was associated with an almost 24-fold risk of HbA1c≥7% compared to the never obese, and there was a 22-fold risk for the more prevalent group with childhood overweight onset. Associations between earlier onset of overweight or obesity and adult HbA1c levels were largely due to the greater adiposity at 45y of those with earlier onset. These findings are important given recent increasing trends in overweight and obesity in many countries. Young children today are overweight earlier in their lives than previous generations, including our cohort.

3. For a minority of individuals, overweight in childhood but not in adulthood, average levels and risk of HbA1c≥6% were not elevated. This finding suggests that detrimental effects of childhood overweight might be averted if BMI gain with increasing age can be controlled. However, those who were obese in childhood and not thereafter had a five-fold risk of HbA1c≥7% or type 2 diabetes, even after adjustment for adiposity at 45y. This finding suggests a long-lasting risk for impaired glucose metabolism in association with childhood obesity even in the absence of adult obesity. Results from our study argue for primary prevention in childhood.

In sum, our study suggests that there are benefits of delaying onset of overweight and obesity, in that risks of elevated HbA1c were lower for 45 year-olds becoming overweight or obese in the previous 12y than for earlier onset. Arguably, therefore, interventions to prevent obesity are best targeted in childhood. Moreover, normal weight groups who gained BMI excessively were at risk of elevated HbA1c (albeit via their attained BMI) suggesting that weight gain across the BMI full distribution should be a focus for preventive strategies for type 2 diabetes.

Physical activity, sedentary behaviour and CVD biomarkers

Prevalence of activity and sedentary behaviour at 45y:
40% of men and 36% of women were identified as most active (moderate vigorous leisure activity frequency ≥6 times/wk, Table 1), in line with comparable data from the Health Survey for England for 2008 (35% of men and 34% of women aged 45y-54y had engaged in non-occupational physical activity on ≥20 days in the last four weeks).

More than one in 5 reported TV-viewing for >3h/day, whilst ~43% reported sitting at work for >3h/day.

In the next stage of our work, we examined associations between activity or sedentary behaviour and CVD biomarkers, as a further pre-requisite for understanding their modifying effects on the obesity - CVD biomarker associations.

We conducted (i) a study for two measures of sedentary behaviour and CVD biomarkers, which was cross-sectional (reflecting data availability); and (ii) a longitudinal study of associations for physical activity and sedentary behaviour over different ages in adulthood in relation to blood pressure and blood lipids in mid-adulthood.

i) Cross-sectional study of associations for two measures of sedentary behaviour (TV-viewing and sitting at work) with biomarkers for CVD and diabetes[output 3]

Several recent studies suggest that sedentary behaviour is associated with mortality and certain diseases or risk factors including obesity, dyslipidemia, metabolic syndrome, type 2 diabetes and high blood pressure. These studies have tended to rely on TV–viewing as a proxy for sedentary behaviour, but there are uncertainties about what this measure represents. TV–viewing could represent a combination of behaviours such as sedentary and dietary habits, as it is known that TV-viewing is associated with dietary behaviour, such as increased energy intake.

Potentially, research to date is important in suggesting that sedentary behaviour and not just lack of physical activity could affect health, implicating independent underlying pathways. But given uncertainties regarding TV-viewing as an appropriate proxy measure, there is a need for further evidence on the role of sedentary behaviour using alternative measures, particularly those representing different domains (e,g. work, commuting, home) apart from leisure.

We sought to establish, therefore, whether (1) associations for (i) TV-viewing and (ii) sitting at work with biomarkers for CVD/diabetes are consistent in direction and magnitude, and (2) TV-viewing and sitting at work are independent risk factors for CVD/diabetes biomarkers. Given current uncertainties about what indicators of sedentary behaviour represent, we examined patterns of association with covariates for the two indicators of sedentary behaviour to establish whether the indicators are related similarly to other factors linked to CVD/diabetes risk.

Patterns of association with covariates:

- first, examining socio-demographic background in relation to our two sedentary behaviour measures we found a trend of increasing percentages of those with manual class backgrounds (childhood and adulthood) and lower educational qualifications from the lowest to the highest h/day TV-viewing. The trend for sitting at work was in the opposite direction, i.e. the percentage with manual class and lower qualifications was highest for those with the lowest h/day sitting at work.

- second, examining lifestyles in relation to our two sedentary behaviour measures we found trends by TV-viewing, with increments in the percentages of those with low fruit and high chips consumption, smoking, infrequent moderate-vigorous leisure activity and obesity from the lowest to highest TV-viewing h/day. Trends in the opposite direction were seen in relation to sitting at work, for all of these lifestyle factors except obesity and leisure physical activity.

Thus, the pattern of behavioural clustering differed for the two sedentary indicators.

Associations for two sedentary behaviour measures and CVD biomarkers:

For women, higher h/day TV-viewing was associated with an adverse profile for all biomarkers except HbA1c, whereas sitting at work was associated with none. In adjusted models, total and LDL cholesterol, triglycerides, SBP and DBP were higher by 0.8% (95% CI: 0.4%, 1.3%) to 4.5% (2.6%, 6.4%) for SBP and triglycerides respectively and HDL

was lower by 2.0% (1.2%, 2.9%) per category increase of TV-viewing (i.e. 0-1, 1-2, 2-3 and >3 h/day). Associations were reduced after adjustment for BMI and diet.

For men, neither TV-viewing or sitting h/day at work were associated with total or LDL cholesterol or HbA1c. Triglycerides, SBP and DBP were higher by 0.4% (0.1, 0.8) to 4.5% (2.3%, 6.6%) for SBP and triglycerides respectively and HDL was lower by 2.3% (1.5%, 3.2%) per increase in TV-viewing category. Associations were attenuated after adjustment for diet and/or BMI. Compared to TV-viewing, associations with sitting at work tended to be weaker (with triglycerides levels higher by 3.0% (1.3, 4.7) and HDL lower by 1.2% (0.5%, 1.9%) per category increase in work sitting time) or not significant (SBP, DBP).

In sum, our study suggests:

- detrimental associations for several CVD biomarkers with each increment (h/day) of TV-viewing but less consistently for sitting at work;
- differing lifestyle and socio-demographic patterns for the two indicators of sedentary behaviour;
- mediation of TV-viewing associations with CVD biomarkers by BMI.

Our findings support an association between sedentary behaviour and CVD biomarkers, particularly for lipids. However, our two measures of sedentary behaviour vary in their association with CVD biomarkers, possibly suggesting that the role of sedentary behaviour varies by domain (with differences in energy expenditure for each behaviour) or because they reflect a differing constellation of factors, past and present, associated with CVD biomarkers.

(ii) longitudinal study of associations for physical activity and sedentary behaviour over different ages in adulthood in relation to blood pressure and blood lipids in mid-adulthood *outputs4,5*

Although the literature is extensive on the role of activity and sedentary behaviour on risk of CVD and diabetes, there are few large longitudinal studies of the general population. Such longitudinal data are needed to establish whether changes or accumulation of (in)activity behaviour predict risk factors for CVD.

Given the scarcity of evidence on long-term associations of (in)activity with CVD biomarkers we examined associations of (in)activity at different life stages with BP and lipid levels in mid-adulthood. We used information on activity and TV-viewing at several ages (23,33,42,45y) and BP or lipids at 45y, examining associations without and with adjustment for covariates, with adjustments staged to identify any mediating role of adiposity.

Blood pressure[output 4]

We examined whether physical activity and sedentary behaviour at different life-stages were associated with BP at 45y. There was little evidence of a trend in BP across frequency of activity, rather there was a threshold associated with (dis)benefit for active vs inactive (e.g. not active in last month at 23y or <2-3 times/month at 33y).

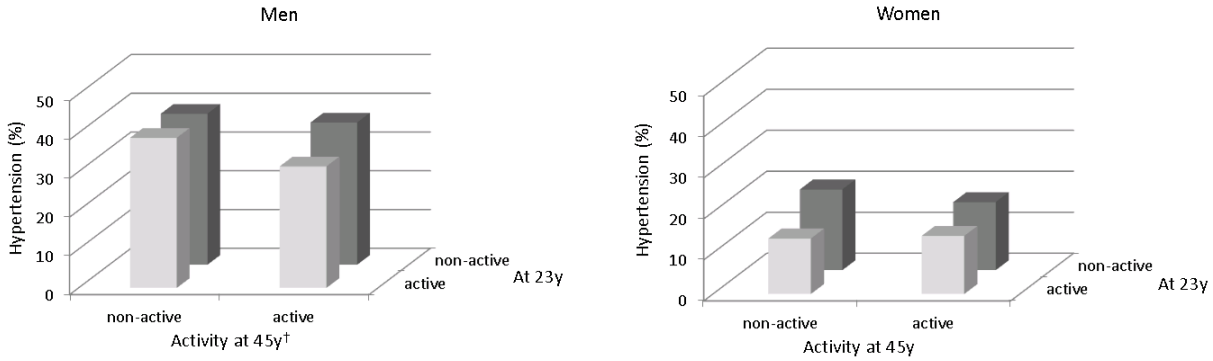
Leisure activity, 23 to 45y, was associated with lower SBP and DBP by ~1-2mmHg and with reduced risk of hypertension about 23% (active vs non-active) depending on activity assessment age. Associations attenuated partially with adjustment, although for active

Table 4: Odds ratios (95% confidence intervals) for hypertension at 45y according to physical activity and sedentary behaviour at different ages[‡]

	Men			Women		
	Model 1[1]	Model 2 [2]	Model 3 [3]	Model 1[1]	Model 2 [2]	Model 3 [3]
Physical activity at ages:						
23y (active vs non-active)	0.82(0.74, 0.91)	0.78(0.69, 0.89)	0.79(0.70, 0.90)	0.73(0.63, 0.84)	0.85(0.71, 1.02)	0.93(0.77, 1.13)
33y	0.85(0.76, 0.95)	0.88(0.77, 1.02)	0.92(0.80, 1.07)	0.77(0.66, 0.89)	0.77(0.65, 0.93)	0.80(0.66, 0.97)
42y	0.73(0.66, 0.81)	0.77(0.68, 0.88)	0.84(0.73, 0.95)	0.88(0.77, 1.01)	1.08(0.91, 1.28)	1.17(0.98, 1.39)
45y leisure[~]	0.79(0.71, 0.87)	0.89(0.78, 1.01)	0.91(0.80, 1.03)	0.79(0.69, 0.91)	0.88(0.75, 1.03)	0.94(0.80, 1.12)
work[†]	1.25(1.12, 1.39)	1.09(0.95, 1.25)	1.15(1.00, 1.32)	1.09(0.94, 1.27)	1.15(0.97, 1.37)	1.10(0.92, 1.32)
Sedentary behaviour						
Sitting at work (h/day) at 45y	0.97(0.95, 1.00)	1.01(0.99, 1.04)	1.00(0.97, 1.03)	1.01(0.98, 1.05)	1.03(0.99, 1.08)	1.03(0.99, 1.08)
TV-viewing at ages						
23y (times/week)	1.08(1.04, 1.12)	1.07(1.02, 1.11)	1.05(1.01, 1.10)	1.06(1.01, 1.11)	1.06(1.00, 1.12)	1.03(0.97, 1.09)
45y (h/day)	1.14(1.09, 1.19)	1.12(1.06, 1.18)	1.06(1.00, 1.12)	1.21(1.14, 1.28)	1.10(1.03, 1.19)	1.01(0.94, 1.09)

[‡] OR for active vs non-active from logistic regression models weighted to N=17,313.
[1] Model 1: adjusted for factors affecting the measurement of blood pressure, i.e. room temperature and time of day.
[2] Model 2: model 1 + gestational age, birth weight, long-term limiting illness, smoking, alcohol drink, dietary factors (fruit, whole bread, margarine, chips, drinking milk), social class at birth and 42y and concurrent activity (for sedentary behaviour) or TV-viewing (for activity).
[3] Model 3: model 2 + BMI at 45y
[~] leisure (≥150 mins/wk) moderate-vigorous activity
[†] work (above median h/day moderate-vigorous)

Figure 2. Prevalence (%)[‡] of hypertension at 45y by activity at two ages in adult life



[‡]Estimated from models adjusted for factors affecting BP measurement, i.e. room temperature and time of day
[†] active=moderate-vigorous leisure activity ≥150 mins/wk

men (vs not active) at 23y, the OR for hypertension of 0.82 (95% CI 0.74, 0.91) changed to 0.79 (0.70, 0.90) after adjustment for covariates including BMI (Table 4).

When modelling activity at early and later adult ages simultaneously, activity at 23 and 45y were independently associated with BP for men. These independent associations suggest that activity over more than one age has an accumulative association with subsequent BP.

Indeed, we found that average BP levels were highest for least active men at both ages and lowest for the active at both ages (for SBP, DBP and hypertension). For example, men least active at both 23y and 45y had the highest prevalence (39.0%) of hypertension; active men (23y) who became least active (45y) had a higher prevalence than those still active at 45y (38.7% vs 31.4%) (Figure 2). Additional contributions of activity at both ages remained in models for DBP and hypertension when adjusted for covariates. Patterns for the combined associations of activity at 23 and 45y were broadly similar for hypertension among women.

- Given that activity in early adulthood was associated with hypertension even after taking account of more recent activity, which was also associated with BP, suggests that there are benefits to adult BP of becoming active and cumulative benefits of sustaining active lifestyles over many years of adult life.

With the observational data available, we cannot establish the direction of association, i.e. whether altered behaviour is a precursor to or consequence of BP levels. Yet, reverse causation is an unlikely explanation for associations with activity at younger ages (e.g. 23y among men) or for the benefits to BP associated with improved activity level. We took account of other health-related factors (e.g. socio-economic position, diet, smoking and alcohol consumption and longstanding illness) proximate in years to BP assessment, but cannot entirely discount the possibility that cumulative associations of activity might be due to improvements in other factors.

Sitting at work was not associated with adult BP after adjustment for covariates and no associations were observed for TV-viewing at 11 and 16y. In adulthood, there was a trend of higher BP with greater time spent watching TV. For example, SBP was higher by 0.54mmHg (men) and 0.35mmHg (women) for each time/week spent watching TV at

23y and risk of hypertension increased by 8% and 6% respectively (Table 4). For both men and women, associations of TV-viewing at 45y with SBP, DBP and hypertension attenuated after adjustment for covariates and most associations were abolished with additional adjustment for 45y BMI; similarly for TV-viewing at 23y among women. Yet for men, associations with TV-viewing at 23y persisted, although diminished: the OR for hypertension of 1.08 (1.04, 1.12) per time/week TV-viewing reduced to 1.05 (1.01, 1.10) after adjustment for covariates and 45y BMI.

When TV-viewing at 23 and 45y were modelled simultaneously, associations with SBP, DBP and hypertension for men attenuated slightly but were not abolished; the independent associations for both ages suggested a cumulative association for TV-viewing. To illustrate, men with low (<1-2 times/week) TV-viewing at 23y who maintained a low level (<1h/day) at 45y had a lower prevalence of hypertension than men who subsequently increased their viewing level (>3 h/day at 45y) (31.2% vs 39.3%); whereas, men with high TV-viewing (>5 times/week) at 23y who subsequently had the lowest viewing (<1hr/day) at 45y had a lower prevalence than those still at higher levels (>3h/day at 45y) (31.2% vs 37.3%). Associations of both 23 and 45y TV-viewing with hypertension among men were little affected after adjustment for covariates. Analyses for women showed associations with SBP, DBP and hypertension of TV-viewing at 45y, but not 23y.

Childhood activity or TV-viewing were not associated with adult BP. The absence of consistent associations for sitting (h/day) at work and BP suggests that sedentary work may be less important than activity, although for both sexes, more frequent and greater hours spent watching TV were associated with higher BP and elevated risk of hypertension.

In sum, our study suggests:

- there are benefits to BP of becoming and sustaining active lifestyles and minimising TV-viewing over many years of adulthood;
- attenuation of most associations with adjustment for BMI suggests a salient mediating role for adiposity in effects of activity and TV-viewing on BP.

Blood lipids[output 5]

In parallel work to that described above for BP, we examined whether activity and sedentary behaviour at different life-stages were associated with blood lipids (total cholesterol, LDL and HDL cholesterol and triglycerides) at 45y.

Activity at different ages was associated with lipid levels, in general, positively for HDL-cholesterol and negatively for triglycerides. To illustrate, a one day/week greater activity frequency at 42y was associated with 0.006mmol/L higher HDL-cholesterol in men and 0.008mmol/L in women and 1.4% lower triglycerides in men (Table 5). Few associations were found for total or LDL-cholesterol.

Most associations attenuated, but were not entirely explained by adjustment for covariates (life-styles and socio-economic factors): e.g., among men, the estimated 2.0% lower triglycerides per one day/week greater activity frequency at 33y reduced to 1.8% after adjustment. But with further adjustment for BMI, most associations were abolished, suggesting a mediating role for BMI (Table 5).

Cumulative associations for activity at different life-stages: there was only limited support for cumulative benefits to lipid levels of activity in early and mid-adulthood.

However, among women, though not men, activity at both 23 and 45y contributed cumulatively to HDL-cholesterol. Women who improved activity from the lowest (none at 23y) to highest level (top quartile of moderate-vigorous activity) had a mean of 1.66mmol/L HDL-cholesterol, compared to 1.53mmol/L for those remaining at the lowest level; those who decreased activity from the highest to lowest had a mean HDL-cholesterol of 1.72mmol/L, compared to 1.78mmol/L for the most active at both ages. Women active at both 23 and 45y had a higher HDL-cholesterol level than those active at one age alone, indicating a cumulative association.

Sedentary behaviour: associations were found for sitting hours at work, negatively for HDL-cholesterol and positively with triglycerides: e.g. a one h/day greater sitting among men was associated with a 0.012mmol/L lower HDL-cholesterol after adjustment for covariates (Table 5). Associations were seen for TV-viewing: e.g., in men, a 0.04mmol/L lower HDL-cholesterol and 5.9% higher triglycerides per h/day greater TV-viewing at 45y, attenuated respectively to 0.03mmol/L and 4.6% after adjustment for covariates. Associations attenuated further after adjustment for current BMI. No cumulative association for TV-viewing at different ages was found.

There was no association between sitting h/day and total or LDL-cholesterol and for TV-viewing associations were weaker and less consistent for these CVD biomarkers.

In sum, our study suggests:

- activity and sedentary behaviour at different adult ages, decades before lipid measurement, were associated with HDL-C and triglycerides in mid-adulthood. Associations of (in)activity with total and LDL-cholesterol were less consistent.
- associations were partly mediated by other life-style factors and by BMI.

Table 5. Associations of physical (in)activity with adult (45y) lipid levels [β(SE)][b]

	HDL-cholesterol			Log_e(triglycerides)[c]		
	Model 1[1]	Model 2[2]	Model 3[3]	Model 1[1]	Model 2[2]	Model 3[3]
Physical activity						
At 23y (times/week)						
Males	0.005(0.003)	0.0002(0.003)	-0.0006(0.003)	-0.008(0.006)	-0.006(0.006)	-0.005(0.006)
Females	0.035(0.005)‡	0.017(0.006)†	0.015(0.005)†	-0.03(0.007)‡	-0.01(0.008)	-0.007(0.007)
At 33y (days/week)						
Males	0.008(0.002)‡	0.005(0.003)*	0.003(0.003)	-0.020(0.004)‡	-0.018(0.005)‡	-0.015(0.005)†
Females	0.001(0.003)	0.0004(0.003)	-0.001(0.003)	0.0005(0.004)	0.001(0.004)	0.004(0.004)
At 42y (days/week)						
Males	0.006(0.002)*	0.002(0.002)	-0.002(0.002)	-0.014(0.004)‡	-0.006(0.004)	-0.0002(0.004)
Females	0.008(0.003)†	0.003(0.003)	0.001(0.003)	-0.002(0.004)	0.004(0.004)	0.0067(0.0035)
At 45y (h/day)						
Leisure: moderate-vigorous activity						
Males	0.005(0.003)	0.002(0.003)	0.001(0.003)	-0.02(0.006)†	-0.01(0.006)	-0.01(0.006)
Females	0.04(0.007)‡	0.02(0.007)*	0.008(0.007)	-0.03(0.009)‡	-0.002(0.010)	0.01(0.009)
Work: moderate-vigorous activity						
Males	0.006(0.002)†	0.009(0.002)‡	0.008(0.002)‡	-0.010(0.004)†	-0.011(0.004)†	-0.010(0.004)†
Females	-0.009(0.004)*	-0.002(0.005)	0.003(0.004)	0.024(0.006)‡	0.014(0.006)*	0.005(0.006)
Sedentary behaviour						
Sitting hours (h/day) at 45y						
Males	-0.008(0.002) ‡	-0.012(0.003)‡	-0.009(0.002)‡	0.011(0.004)†	0.014(0.005)†	0.007(0.005)
Females	0.003(0.004)	-0.007(0.004)	-0.008(0.004)*	-0.001(0.005)	0.009(0.005)	0.009(0.005)
TV-viewing						
At 23y (times/week)						
Males	-0.01(0.003)†	-0.008(0.003)*	-0.005(0.003)	0.015(0.006)†	0.011(0.006)	0.006(0.006)
Females	-0.017(0.004)‡	-0.002(0.004)	0.004(0.004)	0.022(0.005)‡	0.006(0.006)	-0.002(0.005)
At 45y (h/day)						
Males	-0.04(0.005)‡	-0.03(0.005)‡	-0.02(0.005)‡	0.059(0.009)‡	0.046(0.01)‡	0.026(0.01)†
Females	-0.05(0.006)‡	-0.02(0.006)†	-0.003(0.006)	0.076(0.008)‡	0.037(0.009)‡	0.01(0.008)

[b] All models were weighted and corrected for lipids treatment. Regression coefficients (β) represents per unit change in each continuous measure.

[c] Logarithm transformation was used; regression coefficients (β) multiplied by 100 can be interpreted as the % change in triglyceride level associated with one unit change in the independent variable.

[1] Model 1: adjusted for factors affecting lipids measurement (delay of sample receipt and hours since last eating).

[2] Model 2: Model 1 + birth weight, long-term limiting illness, life-style factors (smoking, alcohol drink, diet (i.e. salads, chips, and oily fish)), social class at birth and 42y, concurrent activity (for sedentary behaviour) and sedentary behaviour (for activity); menopausal status, HRT and oral contraceptives (for women).

[3] Model 3: Model 2 + BMI at 45y.

*p<0.05, †p<0.01, ‡p<0.001

Combined and interacting associations between physical activity (or TV-viewing), obesity and biomarkers for CVD and type 2 diabetes [output 1]

Results outlined above for the 1958 birth cohort illustrate the impact of obesity, activity and sedentary behaviour on biomarkers for CVD and type 2 diabetes in this general population sample. Some of our findings, along with other recent research, suggest that obesity, physical activity and sedentary behaviour may have independent associations, i.e. they all contribute, at least to certain biomarker outcomes.

To further understand the extent to which adverse effects of obesity on CVD biomarkers are modifiable by physical activity and sedentary behaviour we investigated the association between obesity in early adulthood (age 33y) with CVD biomarkers at follow-up twelve years later (at 45y) when activity and sedentary behaviour were also assessed. We used measures at these particular time-points to follow, to the extent that it is possible in an observational study, the timing sequence of an activity/sedentary behaviour intervention targeted at obese and non-obese groups. Specifically, we aimed to determine whether:

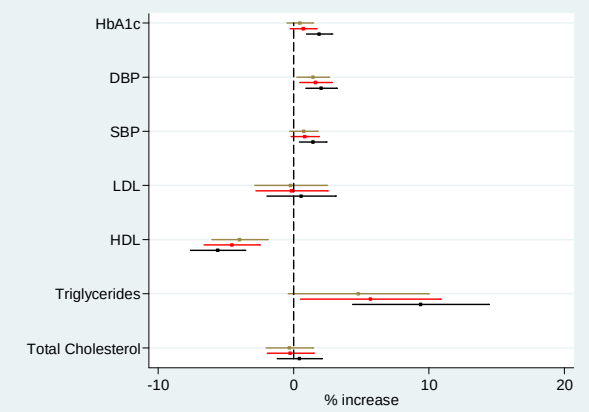
i) obesity, activity and sedentary behaviour were independently associated with several biomarkers for CVD and type 2 diabetes, and

ii) activity or sedentary behaviour moderate the obesity - biomarker associations.

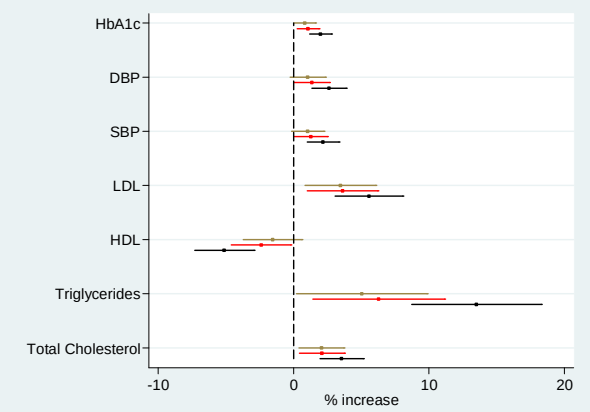
i) Independent associations: For both men and women, obesity at 33y was associated with higher SBP and DBP, HbA1c and triglycerides and with lower HDL cholesterol at 45y, and in women only with higher LDL cholesterol (Figure 1). Associations were largely independent of activity, TV-viewing and other covariates (e.g. diet, smoking, education level) with higher estimated (from adjusted models) levels ranging from ~4% to ~19% in men for SBP and triglycerides respectively and from ~4% to ~27% in women for LDL-cholesterol and triglycerides (Figure 1).

Figure 3: TV-viewing† and CVD/diabetes biomarkers at 45y

a) Men



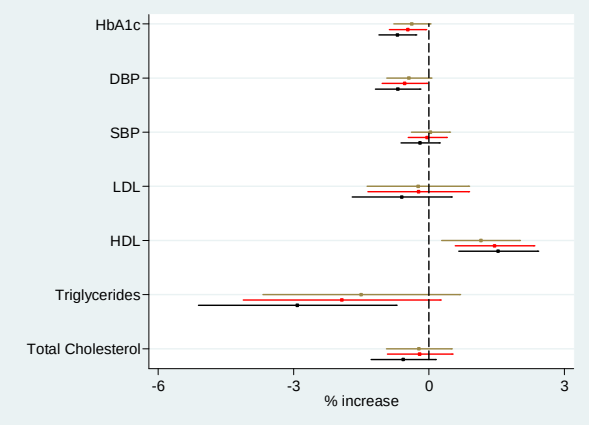
b) Women



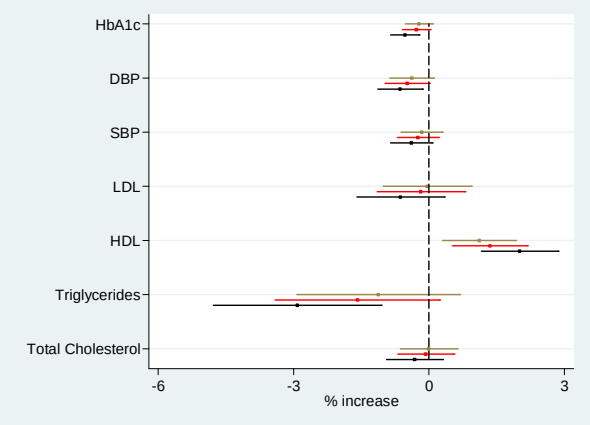
†>3h/day viewing at 45y
Corrected for medication for BP, lipids or T2 diabetes.
Black= Crude associations
Red = adjusted for smoking, SEP, education , limiting daily activity longstanding illness, fruit, chips and alcohol consumption all at 33y + birth-weight.
Additional adjustment for women: HRT, menopausal status and OC use all at 45y.
Additional adjustment for all outcomes except lipids (HDL and LDL cholesterol and triglycerides): total and HDL cholesterol
Additional adjustment for all outcomes except SBP & DBP: Hypertension: yes/no
Brown = Red model + obesity at 33y + PA at 45y

Figure 4: Physical activity and CVD/diabetes biomarkers at 45y

a) Men



b) Women



% increase in biomarker outcomes per unit increase in moderate-vigorous leisure activity frequency at 45y
Corrected for medication for BP, lipids or T2 diabetes.

Black= Crude associations
Red = adjusted for smoking, SEP, education , limiting daily activity longstanding illness, fruit, chips and alcohol consumption all at 33y + birth-weight.
Additional adjustment for women: HRT, menopausal status and OC use all at 45y.
Additional adjustment for all outcomes except lipids (HDL and LDL cholesterol and triglycerides): total and HDL cholesterol
Additional adjustment for all outcomes except SBP & DBP: Hypertension: yes/no
Brown = Red model + obesity at 33y + TV at 45y

Longer TV-viewing was associated with most CVD/diabetes biomarkers, with associations attenuating after adjustment for lifestyles and socio-demographic factors, substantially in some instances, e.g. triglycerides (Figure 3). Yet, TV-viewing was independently (from obesity and activity) associated with some biomarkers, with estimated associations for >3h/day viewing ranging in men from ~4% lower HDL to ~1% higher DBP, and in women, from ~1% higher HbA1c to ~5% higher triglycerides.

Fewer associations with CVD biomarkers were found for activity, and these were largely attenuated after adjustment for covariates (Figure 4).

ii) Moderating associations (interactions): To test interactions of PA (or TV-viewing) with obesity at 33y and CVD/diabetes biomarkers at 45y we used the standard definition for obesity and repeated analyses using the highest 20% BMI.

In general, there was limited evidence of effect modification of the association between obesity and lipids, i.e. interactions with physical activity (or TV-viewing) were non-significant. An exception was for LDL cholesterol, where the detrimental association of TV-viewing was stronger in the non-obese than obese. However, the interaction was borderline ($p<0.06$).

However, some evidence for effect medication was found for HbA1c, for which the beneficial association with increasing frequency of moderate-vigorous leisure activity was stronger for obese than non-obese men, although not women. For both sexes the detrimental association of HbA1c and TV-viewing was stronger for the obese group (p for interactions <0.001).

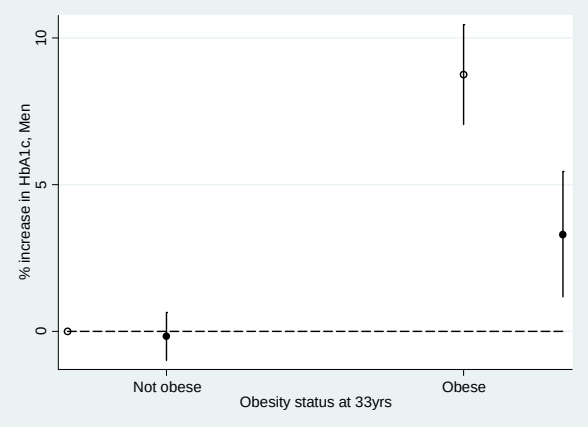
Figure 5 illustrates these associations. In men, no difference in mean % increase in HbA1c levels was observed in the non-obese group, whereas among the obese less active

(moderate-vigorous activity <6 times/wk), HbA1c levels were 8.8% (7.05, 10.45) higher than the reference (non-obese, less active) compared to 3.3% (1.18, 5.45) higher in the more frequently active (i.e. ≥6 times/wk). In women, the higher average HbA1c levels subsequently at 45y associated with TV-viewing among obese compared to non-obese women at 33y is evident from Figure 5b. Whereas HBA1c levels in non-obese women were little affected by TV-viewing, obese women watching >3h/day had higher HbA1c than those viewing for <3h/day.

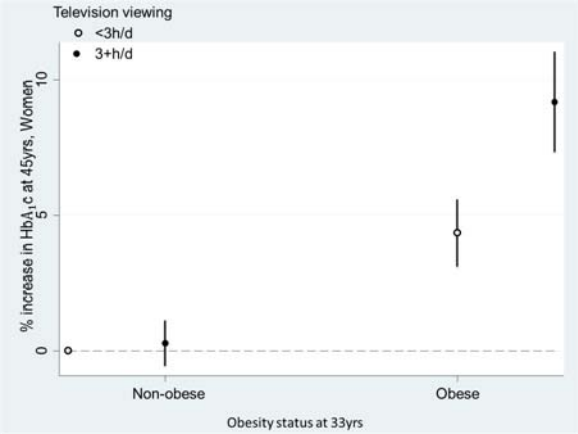
Generally, interactions of PA and TV with obesity (33y) on HbA1c levels at 45y were confirmed in sensitivity analyses using (i) obesity at 42y rather than at 33y, and (ii) central obesity at 45y. The associations observed suggest a greater benefit in obese than non-obese groups of frequent moderate-vigorous activity and a more detrimental effect of higher TV-viewing on HbA1c.

Figure 5: Obesity at 33y and HbA1c at 45y with

a) moderate-vigorous leisure activity, men



b) TV-viewing, women



For BP, there was no interaction of obesity with TV-viewing, but some evidence of interaction with activity. The pattern was similar to that observed for HbA1c, whereby the protective association of activity on BP was stronger for obese groups. Our preliminary analyses in the sample with complete data show interactions in most instances to be borderline. Further weighted analyses have yet to be undertaken.

Additional sensitivity checks are still being completed on the modifying effect of activity or TV-viewing on the association between obesity and CVD biomarkers and work on SEP is in preliminary stages. This work was undertaken towards the end of our PHRC grant, given that it was necessary in the initial stages to build our knowledge of the separate (obesity, activity and sedentary behaviour) associations in this specific population.

Therefore our conclusions are tentative at this stage, but include:

- Our study highlights the importance of obesity, with measures obtained 12y previously at age 33y associated with adverse profiles on several CVD and diabetes biomarkers ascertained at 45y. Associations were mostly independent of activity, TV or other factors.
- Longer (>3h/day) TV-viewing was also associated with several biomarkers, with the suggestion of mediation via adiposity and other factors (e.g. diet).

Associations for physical activity were fewer, and as for TV-viewing, with mediation via adiposity and other factors.

- For glucose metabolism, our findings show effect modification of the association with obesity, suggestive of a greater (i) detrimental association of high (>3h/day) TV viewing, and (ii) benefit of moderate-vigorous activity frequency in obese than non-obese men and women. These results support an argument for changes in these modifiable risk factors (TV-viewing and activity) to lessen the impact of obesity on risk of diabetes.

Additional work *outputs 6,7,8*

We conducted additional work not identified in the original application, as described in ANNEX 2. This work required only minimal input but has resulted in important and relevant outputs. Specifically:

(i) in a study of the intergenerational adiposity association[6] we showed that parent-offspring BMI associations in the 1958 cohort vary by social position.

(ii) in collaborations on relevant genetic studies, we contributed data used to identify (a) new genetic loci for obesity manifest in childhood, and (b) an interaction between activity and FTO variants.

These studies are in part a response to scientific advances occurring since the original application for this project, notably the rapid expansion of knowledge of genetic influences on adiposity. We regard these additional studies as informing and enhancing our study aims and conclusions (see ANNEX 2).

Conclusions. (considerations for policy and research)

This study is based on observational data, with all of the limitations that this imposes, including self-reported measures of activity and changes in these measures at different contacts with study participants. Accordingly, our findings should be interpreted as providing suggestive rather than irrefutable evidence on cause and effect. Nonetheless, the study has considerable strengths owing to its population coverage and longitudinal data, including repeated measurement of BMI from child to adulthood. Importantly, the long period of follow-up within adulthood exceeds that available for many intervention studies. In addition, some strengths of the study design are relevant throughout all of the work, including the availability of, and statistical adjustment for, potential confounding factors *from different life-stages*. For specific studies, such as, the role of activity for blood pressure and blood lipids in mid-adulthood, the ascertainment of activity levels years in advance of biomarker measurement was particularly important. These data may partly overcome the potential problem of reverse causation, whereby obese individuals with adverse biomarker levels reduce their activity.

Activity, sedentary behaviour and biomarkers for cvd: our work on blood pressure, lipids and glucose metabolism (HbA1c) informs the evidence-base on the:

(i) shape of relationships with activity and sedentary behaviour,

(ii) ages (life-stages) that are potentially important and whether there is an effect of activity accumulation or change with age, and

(iii) role of sedentary behaviour vs activity.

The majority of our findings relate to activity and sedentary behaviour in leisure-time, given that this was the primary domain for which information was available from 23 to 45y. Clearly, leisure-time is only one domain of life and others may be relevant. Activity at work, assessed at 45y only, was associated with improved HDL-cholesterol and triglyceride levels in men, but no benefit to BP was found. Similarly, sedentary behaviour at work was also assessed for the first time at 45y, as reported below.

Shape of relationships: in general, associations tended to be linear for blood lipids (specifically, HDL-cholesterol and triglycerides), such that lipid levels increased or decreased per increment in activity (e.g. for each day/week of activity participation at

33y or 42y); whereas for blood pressure, there was little evidence of a trend across frequency of activity, rather there appeared to be a threshold associated with blood pressure (dis)benefit. With the measures available to us, the main distinction was between those active or not active in the last month at 23y or between the least (i.e. <2-3 times/month) vs more active at 33y.

Thus, for blood pressure our work suggests that benefits may be associated with a minimum activity frequency, whilst improvements in HDL-cholesterol and triglyceride levels are likely to be gained incrementally with activity level.

Ages (life-stages), accumulation or change in activity level: for both blood pressure and blood lipids there was some evidence to suggest an influence of activity participation decades before biomarker measurement in mid-adulthood. For example, activity at 23y was associated with risk of hypertension and in women, with HDL-cholesterol levels.

For blood pressure, our study suggested that there are cumulative associations for activity: early adulthood activity was associated with hypertension even after taking account of more recent activity, which was also associated with BP. This suggests that there may be benefits to adult BP of becoming active and cumulative benefits of sustaining active lifestyles over many years of adult life. Whilst activity earlier in adulthood was also associated with lipid levels in mid-adulthood, there was only limited support for cumulative benefits of activity in early and mid-adulthood; notably among women, activity at both 23 and 42y contributed cumulatively to HDL-cholesterol.

Role of sedentary behaviour vs activity: Our research on the 1958 cohort suggests that associations of sedentary behaviour (indexed by TV-viewing) with CVD biomarkers are generally separate from those observed for physical activity. Associations for TV-viewing were also graded, i.e. with biomarker level change with each increment in h/day of TV-viewing. However, associations with CVD biomarkers were less consistent for sedentary lifestyle as indicated by sitting at work. Our results therefore point to the following:

- from a research perspective, there is a need for further understanding of indicators of sedentary behaviour;
- from a disease prevention perspective, TV-viewing provides a simple indicator for other risk factors, many of which are more difficult to measure. Questions remain about whether associations with TV-viewing represent a causal effect of sedentary behaviour but, potentially, reduction in high levels of TV-viewing may have benefits for disease-risk profiles of the population.

Mediation through adiposity: Throughout our analyses of blood pressure, blood lipids and HbA1c, there was evidence that associations of activity and sedentary behaviour were mediated through adiposity. Indeed, few independent associations remained for activity and sedentary behaviour after allowance was made for BMI. This suggests that activity and sedentary behaviour are associated with BMI, which in turn impacts on these CVD/diabetes biomarkers. Associations of activity or TV-viewing with BMI/obesity have been documented for this study population in our previous research (Parsons et al, 2006, 2008).

Obesity and CVD/diabetes biomarkers

Our study highlights the importance of obesity for several biomarkers for CVD and type 2 diabetes in a general population of middle-aged adults.

Type 2 diabetes has long been known to be associated with obesity, and our examination of life-course onset of obesity and BMI change, showed overweight or obesity onset in childhood or young adulthood to be associated with greatest risk of elevated HbA1c, mostly because those with earlier age of onset have the highest mean BMIs and waist

circumference at 45y. These findings are important from a public health perspective, given that young children today are overweight earlier in their lives than previous generations, including our cohort. They argue for primary prevention of obesity in childhood and early adulthood, thereby delaying onset of overweight and obesity.

By studying HbA1c levels of the minority of overweight children who were not overweight in adulthood and showing that their average levels and risk of HbA1c≥6% were not elevated, our study suggests that detrimental effects of childhood overweight can be averted if BMI gain with increasing age can be controlled. Yet, those who were obese in childhood and not thereafter had a long-lasting risk for impaired glucose metabolism (HbA1c≥7%). Confirmation of this finding is needed. It is possible that genetic studies may shed light on this finding, if for example, genetic variants associated with childhood onset of obesity (e.g. as described in ANNEX 2) are also linked to glucose metabolism.

Our study also suggests that there is a greater (i) detrimental association of high TV viewing, and (ii) benefit of physical activity with HbA1c among obese than non-obese men and women. Thus, for type 2 diabetes prevention, reduction of sedentary behaviour (TV-viewing) and promotion of activity and may be especially important for obese groups. This finding resonates with the meta-analytic study finding that physical activity attenuates the influence of FTO variants on obesity (ANNEX 2). Taken together, these findings of modifying associations of (in)activity have implication for public health: (1) suggesting that activity may be an effective control of weight for individuals with a genetic predisposition to obesity, and (2) providing added motivation for obese people to minimise their risk of diabetes or those with a high genetic risk to reduce their obesity susceptibility by being less inactive.

Our project has focussed only on physical activity and sedentary behaviour as potential modifying influences on the association between obesity and CVD/diabetes biomarkers. Further research to improve understanding of how to lessen the impact of obesity on associated disease risk is warranted.

Outputs.

Papers:

[1] Power C, Pinto Pereira SM, Ki M, Law C. Combined and interacting associations between physical activity (or sedentary behaviour), obesity and biomarkers for cardiovascular disease and type 2 diabetes. (*manuscript in preparation*)

[2] Power C, Thomas C. Changes in body mass index, duration of overweight and obesity and glucose metabolism: 45 years of follow-up of a birth cohort. *Diabetes Care*. 2011;34:1986–1991

[3] Pinto Pereira SM, Ki M, Power C. Sedentary behaviour and cardiovascular disease (CVD) risk: Television-viewing vs. sitting at work. (*submitted, under revision*)

[4] Pouliou T, Ki M, Li L, Law C, Power C. Physical activity and sedentary behaviour at different life stages and adult blood pressure in the 1958 British cohort. *Journal of Hypertension* 2011 (in press)

[5] Ki M, Pouliou T, Li L, Power C. Physical (in)activity over 20y in adulthood: associations with adult lipid levels in the 1958 British birth cohort. *Atherosclerosis* 2011;219: 361-367

[6] Power C, Pouliou T, Li L, Cooper R, Hyppönen E. Parental and offspring adiposity associations: insights from the 1958 British birth cohort. *Annals Human Biology* 2011;38:390-399.

[7] Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, Demerath E, Ahmad T, Mora S, Kaakinen M, Sandholt CH, Holzapfel C, Autenrieth C, Hyppönen E, Cauchi S, He M, Kutalik Z, Kumari M, Stančáková A, Meidtner K, Balkau B, Tan JT, Mangino M, Timpson NJ, Song Y, Zillikens MC, Jablonski KA, Garcia ME, Johansson S, Bragg-Gresham JL, Wu Y, van Vliet-Ostaptchouk JV, Onland-Moret NC, Zimmermann E, Rivera NV, Tanaka T, Stringham HM, Silbernagel G, Kanoni S, Feitosa MF, Snitker S, Ruiz JR, Metter J, Larrad MTM, Atalay M, Hakanen M, Amin N, Cavalcanti-Proença C, Grøntved A, Hallmans G, Jansson J-O, Kuusisto J, Kähönen M, Lutsey P, Palla L, Renström F, Scott RA, Shungin D, Sovio U, Tammelin TH, Rönnemaa T, Lakka TA, Uusitupa M, Rios MS, Ferrucci L, C Bouchard, Meirhaeghe A, Fu M, Walker M, Borecki IB, Dedoussis GV, Fritsche A, Ohlsson C, Boehnke M, Bandinelli S, van Duijn CM, Ebrahim S, Lawlor D, Gudnason V, Harris TB, Sørensen TI, Hofman A, Uitterlinden AG, Tuomilehto J, Lehtimäki T, Raitakari O, Isomaa B, Njølstad PR, Florez JC, Liu S, Ness A, Spector TD, Tai ES, Froguel P, Boeing H, Laakso M, Marmot M, Bergmann S, Power C, K-T Khaw, Chasman D, Ridker P, Hansen T, Monda K, Illig T, Järvelin M-R, Wareham NJ, Hu FB, Groop LC, Orho-Melander M, Ekelund U, Franks PW, Loos RJF. Physical activity attenuates the influence of FTO variants on obesity; a meta-analysis of 218,166 adults and 19,268 children. *PLoS Med* 8(11): e1001116. doi:10.1371/journal.pmed.1001116.

[8] Grant S. et al. (The Early Growth Genetics Consortium). A genome-wide association meta-analysis reveals new childhood obesity loci. (*submitted, under revision*)

Presentations:

- * Pouliou T, Ki M, Power C. Physical (in)activity and Body mass index throughout the life-course: impact on adult blood pressure in the 1958 British cohort. *Conference of Epidemiological Longitudinal Studies in Europe. October 2010***,** *Paphos, Cyprus.*

- * Ki M, Pouliou T, Power C. Physical activity and TV viewing over 20y in adulthood: associations with adult lipids levels in the 1958 British birth cohort. *Conference of Epidemiological Longitudinal Studies in Europe. October 2010***,** *Paphos, Cyprus*

- * Power C, Pouliou T, Cooper R, Hyppönen E. The parent-offspring association in Body Mass index: understandings from in the 1958 British cohort**.** *Conference of Epidemiological Longitudinal Studies in Europe. October 2010***,** *Paphos, Cyprus*

- Power C, Pouliou T, Cooper R, Hyppönen E. Parents and offspring: the adiposity association: insights from the 1958 British birth cohort. (Invited lecture) Symposium on 'Intergenerational and familial influences on obesity and related conditions' organised on behalf of the *Society for the Study of Human Biology and the Biosocial Society*. Durham, Sept 2010

Pinto Pereira SM, Ki M, Pouliou T, Power C. Associations between two measures of sedentary behaviour and cardiovascular, hemostatic and diabetic markers in mid-adult life (45y). *Royal Society of Public Health*, Sept 2011

** Pinto Pereira SM, Ki M, Pouliou T, Power C. Sedentary behaviour and markers of cardiovascular disease and diabetes in mid-adult life (45y). *Society Social Medicine Annual Scientific Meeting*. Warwick, Sept 2011

Abstracts

* Peer-reviewed abstracts selected for oral presentation, included in a special edition of the journal '*Longitudinal and Lifecourse Studies (LLCS)*'.

** Pereira SMP, Ki M, Pouliou T, Power C. Associations between sedentary behaviour and cardiovascular, hemostatic and diabetic markers in mid-adult life (45y). J Epidemiol Commun H 65: Sep 2011.Reporting date: 01 Sep 2011

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ANNEX 1

Data; measures and collection methods

Biomarkers for CVD and diabetes.

We focused on well-described biomarkers from information (including a blood sample) collected by nurses during a home visit with participants at 45y, including:

- blood pressure - three measures were obtained with the participant rested for 5mins; a large cuff was used when mid-upper arm circumference $\geq$32cm. Average SBP and DBP for men at 45y were 132.9 and 82.1mmHg respectively; 120.3 and 75.6mmHg for women. A quarter of the population (34.6% of men; 13.6% of women) were identified as hypertensive, defined according to the World Health Organization guidelines as SBP of ≥140 mmHg or DBP of ≥90 mmHg or current medication for high BP.
- blood lipids were measured from a non-fasted venous blood sample. Total cholesterol and triglycerides, two major serum lipids, and HDL-cholesterol, cholesterol fractions within the lipoprotein, were measured using enzymatic methods. LDL-cholesterol was quantified using the Friedewald equation.
- Glycosylated haemoglobin (HbA1c) and diabetes medication data at 45y. Risk of type 2 diabetes was identified from(i) self-reports at 42y that a doctor had told them that they had "non-insulin-dependent diabetes that is controlled by diet or tablets; (ii) oral anti-diabetic drugs at 45y (BNF code 060102); and (iii) HbA1c≥7.
- Medications were recorded, e.g treatment for blood pressure, diabetes and lipid lowering drugs.

Other factors affecting biomarker measurement (e.g. temperature, blood sampling time, time since last meal) were recorded by the nurse.

Genetic information: extraction of DNA was performed for ~8000 participants at 45y who had given their consent; genomewide data are now available for the majority of these participants.

Body size.

Height and weight was measured at several ages in childhood (7,11,16y) and adulthood (33 and 45y); self-reports were obtained at ages 23y and 42y. Standardised protocols were used for these measurements. For example, at 45y standing height was measured using a Leicester portable stadiometer placed on a hard floor; participants were unshod, lightly clothed and stood upright with their head in the Frankfort plane. Weight was measured to the nearest 0.1kg with shoes removed.

The primary indicator of body size was Body mass index (BMI, kg/m^2), from which obesity was defined, separately at each age, using international BMI cut-offs for child and adulthood (i.e. corresponding to ≥25 kg/m^2 for overweight; ≥30 kg/m^2 for obesity).

Waist and hip circumferences were also measured, but only at age 45y (measured to the nearest 1mm at the point midway between the costal margin and iliac crest (waist) and the widest part of the body below the waist (hip)).

Physical activity.

Levels of physical activity were ascertained by questionnaire, the only feasible method in large population samples; importantly, questions are broadly comparable across particular adult ages.

Measures are as follows:

- participants responded to a single question on frequency of sports participation at 23y, and of regular physical activity at 33y and 42y. As an aid to recall, the question at 33y and 42y provided examples of activities (not at 23y). Categories ranged, at 23y, from '5+ times /week', to 'not at all in the last 4 weeks' and at 33y and 42y, 'most days' to '<2-3 times /month'.
- at 45y activity was estimated with a modified version of the EPIC-Norfolk physical activity questionnaire *(*EPAQ-2) (Wareham et al, 2002). As described elsewhere (Parsons et al, 2009) participants were asked to specify type, duration and frequency of any activities during the last year from a list of 35 leisure and 9 work activities. Three measures were derived for leisure and work activity separately: (i) total duration (h/day) was calculated from summing time (frequency and duration) spent on each activity; (ii) energy expenditure (MET h/day) was quantified as hours spent on each activity multiplied by its MET (metabolic equivalent) value, which refers to energy requirements relative to resting state and (iii) h/day of moderate and vigorous activity (i.e. the sum of any activities with MET values ≥3). A binary variable was generated (i.e., more vs <150 mins/week) corresponding to the current recommendation for moderate intensity activity (30 mins, five times a week) (Dept of Health, 2004; Thompson et al, 2003). The studies of blood pressure and lipids use this definition of leisure activity, as in related publications. However, most of the analyses included in the report use a 5-category variable for moderate-vigorous leisure activity, with categories: none in the last year, once a month or less, less than 3 times/wk, 3-5 times/wk and ≥6 times/wk.
- activity in childhood (11y and 16y) was indicated by questions on frequency of outdoor or indoor sports, use of parks, recreation grounds and swimming pools. We have previously combined these activities to give a single 4 category variable with individuals classified as least to most active.

Sedentary behaviour

- Sitting as work: at 45y as part of the EPAQ-2 questionnaire (work activity questions) participants reported how many hrs/ week they spent sitting work.
- TV-viewing was reported at 23y as frequency (6 categories, from '5+ times /week', to 'not at all in the last 4 weeks'); at 45y, TV-viewing was reported in 6 categories from none to >4h/day. Frequency of TV-viewing at 11 and 16y was categorised as often, sometimes or never/hardly ever).

Potential confounding factors; information spanning child to adulthood includes: parental BMI; early life factors, such as birth-weight, gestational age; infant feeding method; childhood BMI; frequency of consumption of different foods, alcohol intake and smoking as reported at more than one adult age; health status in early adulthood. Information was used on socio-economic position in childhood (e.g. based on father's occupation) and in adulthood (based on the participant's own occupation).

Data limitations: Physical activity and sedentary behaviour were ascertained via self-report. Whilst, questionnaire based measures may be informative (Warren et al, 2010), the precision of exposures is likely to be affected by measurement error. For sedentary behaviour, we used television-viewing as an indicator of leisure-time behaviour using responses in pre-defined categories (h/dy). Television-viewing may be inadequate for leisure-time behaviour if individuals spend large amounts of time in other sedentary actives (e.g. computer use). In this cohort of middle-aged adults, >75% used computers in leisure for <1h/dy, hence, it may be less of an issue here than for younger generations involved in a broader range of behaviours from this domain. there are short-comings also for other data ascertainment methods. For sedentary behaviour at work also, we used reported estimates of the total h/wk respondents sat doing light work. Thus, again our measure is potentially affected by measurement error. However, objectively measured (i.e. accelerometer) data alone do not identify the domains in which behaviour occurs, which may be of potential importance. It has been argued that both domain-specific and overall (objective) measures of sedentary time are desirable (Healy et al, 2011). Likewise, for physical activity, imprecision in our measures may affect study findings,

e.g. for interaction effects. As with alternative designs, not all study short-comings can be addressed, hence our findings should be interpreted as providing suggestive evidence on associations of interest.

Data analysis strategy

Most CVD biomarkers were modelled as continuous outcomes, transformed where necessary, for each risk factor separately, with examination of whether associations are linear. Dichotomous outcomes were also used in some instances (e.g. hypertension or diabetes risk). In general we followed stages of analysis, to examine:

1. the association between obesity and CVD biomarkers;
2. the association between (in)activity and CVD biomarkers;
3. whether there is an interaction between adult obesity and activity (or sedentary behaviour) on CVD biomarkers.

In several analyses we tested independence of associations by simultaneous modelling, e.g of obesity, activity and TV-viewing on each biomarker. We examined modification of the association between obesity and CVD biomarker by activity (or sedentary behaviour) using an interaction term (e.g. TV-viewing *obesity).

We considered full use of the life-course data in respect of confounding factors and used statistical adjustments for such factors using appropriate multivariable regression techniques. Confounding and mediating factors were selected as appropriate for the outcome and the specific purpose of the analysis being undertaken. In general, we considered the effect on associations of factors potentially affecting measurement of outcome, such as room temperature for blood pressure. In most analyses we adjusted for life-time socio-economic position (SEP), as represented by social class in childhood and also in adulthood. Adjustments for SEP were undertaken on the grounds that it is associated with several adult biomarker outcomes in this population (Power et al, 2007) and also with several lifestyle factors. In addition, we usually took account of other lifestyle factors (e.g. diet) in separate models in order that the effects of such adjustments could be identified.

Where appropriate we undertook sensitivity analyses to check the robustness of our findings. For example, when investigating the combined and interacting associations between activity (or sedentary behaviour), obesity and biomarkers for CVD and type 2 diabetes, main analyses were conducted using obesity at 33y, with sensitivity analyses run using (i) obesity at 42y and (ii) central obesity at 45y, rather than 33y. In most analyses, we tested whether effects observed varied by gender by including an interaction term.

In addition, we considered the effect of sample attrition in most studies and in some instances used multiple imputation or inverse probability weighting methods to allow for potential biases relating to missing data. Previous work had suggested that the sample had remained broadly representative of those born in Britain in 1958 (Atherton et al, 2008). Comparing the social class composition of the sample with data in the 45y survey and the original birth sample, fewer participants were from an unskilled manual class (IV&V) in childhood, compared to the original sample: respectively 22.3% and 24.7%. Thus, biases appeared to be small. However, attrition of the study sample over time has the potential to bias findings, with the sample available for analysis reducing as the number of variables (and ages) required for analyses increases. We have therefore undertaken analyses, first using the most limited dataset available (i.e. those with complete data on all variables) and secondly, using imputed or weighted data (based on characteristics associated with non-response). Results have been similar for both sets of analyses and we have presented imputed or weighted results in papers prepared for publication and in this report (except for 'Combined and interacting associations between

physical activity (or sedentary behaviour), obesity and biomarkers for CVD and type 2 diabetes'[1] where weighted/imputation analysis has yet to be undertaken).

A further methodological issue that we addressed in our analyses was the correction for medication effects on CVD biomarkers. Methodological developments on the handling (correcting for) medication effects in epidemiological studies have recently been described by Tobin et al (2005). Commonly used methods (such as adjustment or omission of treated groups) were shown to be unsatisfactory solutions and so we have followed Tobin et al (2005) recommendations for BP work (by adding a correction of 10mmHg to both SBP and DBP for those participants (4.6%) on BP treatment for high BP) and sought appropriate correction factors for lipid-lowering drugs (reducing total cholesterol by 20%, LDL-cholesterol by 35%, triglycerides by 15%, and increasing HDL-cholesterol by 5%, as based on average efficacy of statin, the most frequently prescribed lipid-lowering drug in this cohort)**.** In more recent analyses we have also included a correction for oral anti-diabetic medication for type 2 diabetes (reducing HbA1c levels by 1% in absolute terms (Bennett et al, 2011)).

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ANNEX 2

As mentioned in the main report, we undertook additional work where there was an opportunity to inform and enhance our study aims and conclusions. In particular, we did not wish to disregard scientific advances occurring since the original application for this project, particularly in genetics and interactions with environmental factors, including activity. Our additional work includes:

(i) contributions to relevant genetic studies on genetic loci for obesity manifest in childhood[8], and interaction between activity and FTO variants[7].
(ii) a study of the intergenerational adiposity association[6].

- Genetic studies

There has been an explosion of genetic research identifying an increasing number of variants associated with many diseases. The genome-wide association studies (GWAS) contributing to this identification require large sample sizes, providing the impetus for investigators involved with individual study populations to join large collaborations focussed on specific phenotypes.

Given the focus of our project, we took advantage of opportunities that were most directly related to our study, including the:

(i) study of childhood obesity in the Early Growth Genetics (EGG) Consortium, and
(ii) meta-analysis of physical activity * FTO variants on obesity.

(i) Early Growth Genetics (EGG) Consortium study of childhood obesity *output 8*

In work on obesity and glucose metabolism, described in the main report, individuals who were obese in childhood and not thereafter had a five-fold risk of HbA1c≥7% or type 2 diabetes, even after adjustment for adiposity at 45y, suggesting a long-lasting risk for impaired glucose metabolism in this group. One potential explanation is that there may be common genetic factors for obesity that manifests in childhood and risk of type 2 diabetes.

We therefore contributed to a GWAS seeking to identify novel genetic factors that influence early-onset obesity. Meta-analysis was performed of genome-wide genotyped datasets from 14 study sites consisting of cases who were ≥95th percentile of BMI achieved before age 18 y (N=5,530) and controls, <50th percentile of BMI consistent throughout all child measures (N=8,318) of European ancestry. The study found variation at seven loci, all of which had been reported previously in GWAS for adult BMI. Taking forward analysis of novel signals in replication datasets has revealed at least two novel obesity loci.

This and future work is likely to uncover whether common genetic variants exist for early-onset obesity and risk of type 2 diabetes. Write-up of the research for journal publication is well-advanced and dissemination at academic conferences is planned on behalf of the EGG consortium.

(ii) meta-analysis of physical activity * FTO variants on obesity *output 7*

The aim of this study was to examine whether previous reports in the literature suggesting that PA may attenuate the effect of FTO on BMI (FTO gene harbors the strongest known susceptibility locus for obesity) could be validated. Meta-analysis was performed of 45 studies of adults (n=218,166) and 9 of children and adolescents (n=19,268), with PA standardized as a dichotomous: inactive vs. active. The major finding was to demonstrate that PA and FTO interact on BMI. The BMI-increasing effect of

rs9939609 minor allele was found to be 30% smaller in physically active than in inactive adults.

Public health implications of the finding that physical activity attenuates the influence of FTO variants on obesity were identified as:

- Activity may be an effective control of weight for individuals with a genetic predisposition to obesity at the FTO locus.
- Could motivate people who are identified as having a high genetic risk to reduce their obesity susceptibility by being physically active.

Individuals at high genetic predisposition to obesity are offspring of parents who are obese, as discussed in the following section.

- Parent and offspring adiposity association *output 6*

Parent-offspring adiposity associations are well-established: offspring of obese parents have elevated risks of overweight/obesity. We undertook a review of all studies on intergenerational adiposity associations conducted previously based on the three generations of the 1958 birth cohort. As part of this review we included new analysis (part of the PHRC project) of the parent-offspring BMI association stratified by social class.

The aim of this review and the additional new analysis was to gain insights into explanations for the parent-offspring adiposity association, such as whether parent-offspring BMI associations are due to offspring lifestyles, or depend on socio-economic conditions.

For the three generations in the cohort, we used the notation of G1 for parents, G2 for the cohort and G3 for children of the cohort.

BMI of G1 and G2 were correlated both when offspring were children and in mid-adulthood: a 1kg/m^2 higher parental BMI was associated with an average 0.24 to 0.35 kg/m^2 higher offspring (mothers/fathers vs sons/daughters) BMI at 45y. Associations were little affected by adjustment for lifestyle and socio-economic factors, but varied by social class: average BMI gain in offspring relative to parents was greater in lower classes, e.g. for males vs fathers by 3.6 and 2.5 kg/m^2 in classes IV&V and I&II respectively. Parent-offspring BMI associations were stronger for recent (G2 and G3) than older (G1 and G2) generations.

That the magnitude of the intergenerational BMI association varied by socio-economic origins, suggests that the association is not solely an outcome of genetic influences even though socio-economic origins and related offspring adult lifestyles did not explain the association in this population. Our findings suggest that intergenerational transmission of adiposity may be due to an inter-play between genes and obesogenic environments. Variability (e.g. by socio-economic origins and over time) of intergenerational BMI associations suggests that they are likely to be modifiable. Identification of the conditions affecting the variability of the intergenerational association could therefore provide clues for the promotion of less obesogenic environments.

Parent–offspring associations may contribute towards an amplification of population levels of obesity, in that offspring with increased risks of fatness have elevated risks of adult obesity and in turn their own offspring have a greater likelihood of overweight and obesity. To avoid the perpetuation of an intergenerational cycle (and associated disease risks) policies will be needed to reduce adiposity among the offspring of obese parents. Offspring of obese parents are therefore an important target for interventions aimed at reducing population levels of overweight and obesity.

In sum, parent-offspring associations in BMI were not explained by offspring lifestyles, but varied over successive generations and by social class, suggesting that intergenerational transmission of adiposity at a population level is modifiable rather than immutable.