Contribution of physical activity to the increased risk of type-2 diabetes in UK South Asians compared to Europeans.

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Declaration of originality

I, Saima Afaq, confirm that the work presented in this thesis is original and my own. Where information has been derived from other sources, this has been appropriately referenced.

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Dedication

I lovingly dedicate this work to my daughters, Fatima and Zara, and the memory of my late sister, Bino. I am grateful to my parents, Hafiz Habib Ullah and Kausar Habib, for their unconditional support and prayers. I am thankful to my husband, Mian Afaq Ahmad for his motivation and support.

I am grateful to Professor John Chambers for providing me the opportunity to contribute to the LOLIPOP study. My thanks and appreciation to him for persevering with me for the time it took to complete this research. I thank him for his careful supervision of my thesis and for reading and critiquing drafts of each chapter. His constructive advice has been invaluable. I am thankful to him for his mentorship, kindness, and friendship and most of all an unrelenting belief in my ability. I am grateful to him for providing me support when I most needed it. No words are enough to thank him. I have been extremely lucky to have a supervisor who cared so much about my work, and who responded to my questions and queries so promptly.

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Abstract

Background. South Asians have ~3 times excess risk of T2D and related metabolic disturbances compared to Europeans. The known dietary, adiposity and genetic risk factors do not explain this excess risk of T2D in South Asians compared to Europeans. Contribution of physical activity to the increased T2D risk in South Asians remains undetermined.

Methods. I determined the accuracy of three physical activity accelerometers amongst South Asians and Europeans. I estimated physical activity levels amongst UK South Asian and European men and women, using accelerometers, and investigated the association of physical activity with T2D, insulin resistance and related glycaemic disturbances by using univariate and multivariate analyses.

Results. Energy expenditure Measured by the three accelerometers, in all the positions evaluated, was lower compared to Actual energy expenditure. Difference between Measured and Actual energy expenditure was smallest for the Actigraph GT3X+ in the ankle position compared to all other device-position combinations, amongst both South Asians and Europeans. Total physical activity, as determined by Actigraph GT3X+, was ~31% lower amongst South Asians compared to Europeans (P=0.01). After adjusting for age, sex and adiposity, an increase in physical activity was associated with reduced risk of T2D, insulin resistance and associated glycaemic disturbances (all P<0.05). Incidence of T2D was 13.4% amongst South Asians and 4.6% amongst Europeans in the LOLIPOP cohort over mean 9 years' follow-up (P<0.001). The age, sex and adiposity adjusted relative risk of T2D reduced from 3.3 (95% CI: 2.9-3.7, P=1.1 x 10^{-75}) to 2.3 (95% CI: 2.0-2.7, P=4.5 x 10^{-35}) after adjusting for total physical activity levels. The T2D population attributable risk (%) for achieving less than 600 MET.minutes per week was ~16% in South Asians and ~37% in Europeans.

Conclusions. The results show that accelerometers are as effective in measuring physical activity in South Asians as they are in Europeans and Actigraph GT3X+ is the most accurate device for measuring physical activity in the two populations. My findings suggest the potential for increased physical activity to improve glucose metabolism and insulin resistance, which predict T2D risk, amongst South Asians and help reduce their excess risk of T2D and its related complications. However, an increase in physical activity alone is unlikely to bridge the 3-fold excess risk of T2D in South Asians compared to Europeans.

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List of abbreviations

ADA	American Diabetes Association
ANOVA	Analysis of variance
ACSM	American college of sports medicine
AHA	American Heart Association
BMI	Body mass index
BMR	Basal metabolic rate
CI	Confidence intervals
DCCT	Diabetes control and complications trial
DGI	Diabetes Genetics Initiative
DIAGRAM	Diabetes Genetics replication and Meta-analysis Consortium
DNA	Deoxyribonucleic Acid
DPP	Diabetes Prevention Program - America
FFA	Free fatty acid
FPG	Fasting plasma glucose
FUSION	Finland-US investigation of non-insulin dependent diabetes mellitus
GLUT	Glucose transporter
GWAS	Genome-wide association study
HbA1c	Glycohaemoglobin
HOMA	Homeostasis model of assessment
HSE	Health survey of England
IDDM	Insulin dependent diabetes mellitus
IDDP	Indian diabetes prevention program
IDF	International Diabetes Federation

IFG	Impaired fasting glucose
IGR	Impaired glucose regulation
IGT	Impaired glucose tolerance
IRS	Insulin receptor substrate
LOLIPOP	London Life Sciences Population Study
LTPA	Leisure time physical activity
MAGIC	Meta-Analyses of Glucose and Insulin related traits Consortium
METs	Metabolic equivalents
MODY	Mature onset diabetes of young
MUFA	Monounsaturated fatty acid
NCD-RISC	Non-communicable disease risk factor collaboration
NGSP	National Glycohaemoglobin standardisation program
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAL	Physical activity level
PAR	Population attributable risk
PI-3	Phosphoinositol kinase - 3
PKB	Protein kinase B
PROMIS	Pakistan Risk Factors of Myocardial Infarction Study
PUFA	Polyunsaturated fatty acids
RMR	Resting metabolic rate
SABRE	Southall and Brent Revisted
SD	Standard deviation

SFA	Saturated fatty acid
SINDI	Singapore Indian Eye Study
SNP	Single nucleotide polymorphism
SOS	Swedish obesity subjects
T2D	Type-2 diabetes
TEE	Total energy expenditure
TFA	Trans fatty acid
UK	United Kingdom
UK PDS	United Kingdom Prevention of Diabetes Study
USDHHS	United States department of health and human sciences
WHO	World Health Organization
WHR	Waist-hip ratio
WTCCC	Wellcome Trust Case Control Consortium

Chapter 1: Literature review

1.1. Search strategy

I conducted a five-staged comprehensive search of the literature in the following databases; PubMed® (U.S. National Library of Medicine, USA), Web of Science® [v.5.4] (Thomson Reuters, USA) and SciVerse Scopus® (Elsevier Properties S.A, USA) for studies published before 1st December 2016. During the first stage the above databases were searched using combinations of following keywords 'Exercise', 'Walking', 'Physical activity', 'Inactivity', 'Physical Activity Questionnaire', 'International Physical Activity Questionnaire', 'IPAQ', 'Global Physical Activity Questionnaire' and 'GPAQ', 'Energy expenditure', 'PA', 'physical exercise', 'physical fitness', 'exercise', 'sport', 'physical training', 'recreation activity', 'MVPA', 'LTPA', 'TPA', 'leisure activities', 'sedentary behaviour', 'diabetes', 'Type 2 diabetes', 'T2D', 'insulin resistance', 'hyper glycemia', 'South Asians/immigrants', South Asia', 'Sri Lanka', 'India', 'Bangladesh', 'Pakistan'.

In the second stage, the total hits obtained from searching these three databases were pooled together and duplicates were removed. This was followed by screening of the retrieved articles by reading the article title in the third stage and abstracts in stage four. In the fifth stage, individual manuscripts were screened. To obtain additional data a manual search of the reference lists of articles selected in stage five was performed. Wherever possible forward citations of the studies retrieved during the literature search was traced. Furthermore, data were also retrieved from the search of relevant web sites and online resources.

Inclusion criteria

The following inclusion criteria were used; a) Population-based studies among human adults (>18 years of age), b) Cross–sectional study design or being the first phase of a longitudinal study, c) Geographically and temporally defined population

from any of the South Asian countries mentioned above, d) Being an original study presenting data on above mentioned terms, e) Evaluating physical activity using questionnaires, f) Published in English g) Peer-reviewed fully published research papers h) Systematic reviews on physical activity and T2D in South Asians populations and i) Studies comparing physical activity and T2D between South Asian populations and Europeans.

1.2. Introduction

Diabetes is one of the most common causes of death[1], responsible for 5 million deaths worldwide in 2015 (IDF Annual Report 2015)[2]. Approximately 90% of all the adults diagnosed with Diabetes have Type 2 Diabetes (T2D). T2D is an established risk factor for cardiovascular disease[3], the leading cause of death globally, particularly in South Asia (India, Pakistan, Bangladesh and Sri Lanka)[4]. About one-quarter of the world's population is South Asian, and South Asians also represent the fastest growing migrant population in many developed countries of the world including UK. South Asia represents one of the largest populations of people with T2D[5,6]. By 2040, it is projected that the number of people affected with T2D in South Asia will increase by ~55% compared to the predicted ~20% increase in Europeans[2]. In the UK, the prevalence of T2D is ~20% amongst South Asians compared to ~6% in Europeans[7]. South Asia is, therefore, a major contributor to the rapidly emerging T2D epidemic globally. An understanding of the possible risk factors, associated with T2D development, in South Asians is important for earlier implementation of prevention measures in this population, with the potential for reversing global T2D epidemic and improving global public health. The mechanisms underlying the increased risk of T2D among UK South Asians remain to be determined[8,9]. Physical inactivity is recognized as a major risk factor for T2D. Previous studies suggest that; UK South Asians have

lower physical activity levels compared with Europeans[10-12]. However, the contribution of physical activity levels to T2D in UK South Asians remains to be determined[13-15].

1.3. Definition of T2D

Type 2 diabetes is a metabolic disorder characterized by high blood glucose levels in the setting of insulin resistance and pancreatic beta cell dysfunction[16-18]. Increased insulin resistance typically occurs first, leading to hyperglycaemia, an increase in pancreatic insulin secretion, and hyperinsulinaemia. This is followed by progressive loss of pancreatic beta cell function, a relative deficiency of insulin and progression to clinical T2D[16].

Diabetes was first classified by World Health Organisation (WHO) in 1980 into two main types: Type-1 Diabetes/Insulin dependent Diabetes mellitus (IDDM) and Type-2 diabetes/Non-insulin-dependent diabetes mellitus (NIDDM). Other recognised classes of diabetes include: gestational diabetes, diabetes due to specific genetic defects in pancreatic beta-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (cystic fibrosis), and drug/chemical induced diabetes (such as in the treatment of AIDS or after organ transplantation).

Diabetes is diagnosed by determining the blood glucose levels. Biochemical tests for diagnosing diabetes include fasting plasma glucose (FPG) levels, oral glucose tolerance test (OGTT) and Glycohaemoglobin (HbA1c) test. WHO Criteria for the diagnosis of T2D is described in **table 1.1.**

Table 1.1 Definition of T2D according to the World Health Organisation (WHO) and American Diabetes Association (ADA).

Investigation	T2D diagnosing criteria
Fasting plasma glucose	**> 7.0 mmol/l** Fasting is defined as no caloric intake for 8 hours.
Random plasma glucose	**>11.1 mmol/l** Valid in patients having classic symptoms of hyperglycaemia or hyperglycaemic crisis.
Two-hour plasma glucose	**>11.1 mmol/l** The test should be performed using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.
HbA1c	**>6.5% (47.5 mmol/mol)** The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

1.4. Impaired glucose regulation (IGR)

Impaired glucose regulation (IGR) or pre-diabetes refers to an intermediate state of abnormal glucose regulation where blood glucose levels are above the normal range but are not high enough for the diagnosis of T2D.

IGR can be described as impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). IGR is asymptomatic and can remain undiagnosed for many years. According to American Diabetes Association (ADA) both IFG and IGT constitute a “pre-diabetic” state and HbA1c values of 5.7-6.4% (38.8 – 46.4 mmol/mol) define pre-diabetes. IFG is defined as fasting plasma levels of 5.6-6.9 mmol/l and IGT as glucose levels of 7.8-11.0 mmol/l 2 hours post OGTT. The WHO defines pre-diabetes based on HbA1c as 6.1 – 6.4% (42.1 – 46.4 mmol/mol). IFG is defined as fasting plasma glucose levels between 6.1 – 6.9mmol/l, while it retains the same criteria for the diagnosis of IGT as ADA (**table 1.2**).

Table 1.2 Definition of Impaired Glucose Regulation according to WHO and ADA criteria.

	Criteria
World Health Organisation (WHO)	
Fasting plasma glucose (mmol/L)	6.1 – 6.9
Two-hour oral glucose tolerance test (mmol/L)	7.8 – 11.0
HbA1c (%, mmol/mol)	6.0 – 6.4, 42.1 – 46.4
American Diabetes Association (ADA)	
Fasting plasma glucose (mmol/L)	5.6 – 6.9
Two-hour oral glucose tolerance test (mmol/L)	7.8 – 11.0
HbA1c (%, mmol/mol)	5.7 – 6.4, 38.8 – 46.4

1.5. Epidemiology of T2D

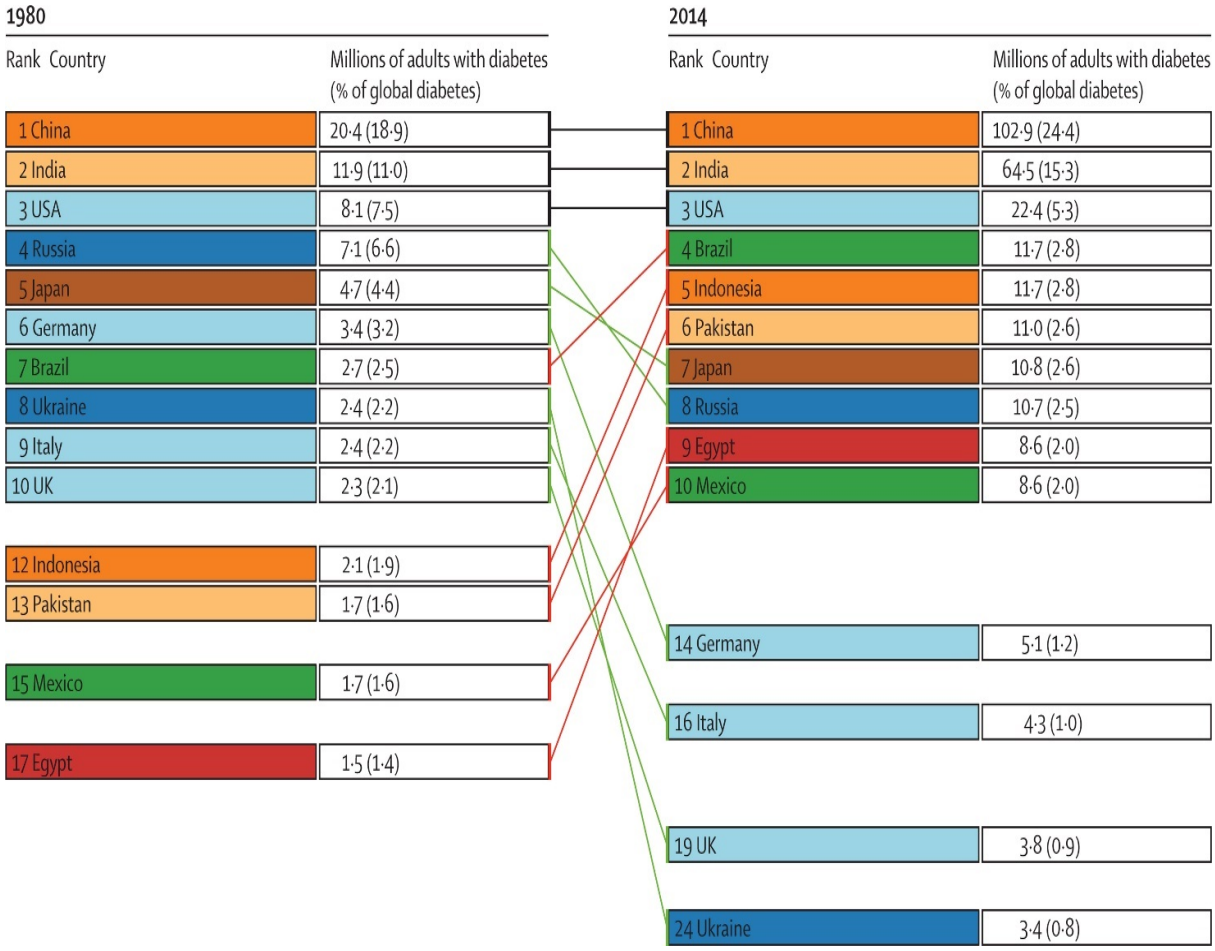
1.5.1. Global burden of T2D

Type 2 Diabetes is one of the leading global health hazards and is a major risk factor for cardiovascular disease and microvascular complications such as retinopathy, neuropathy and nephropathy[19]. According to the IDF, in 2015, there were an estimated 415 million people with T2D, and T2D was estimated to underlie approximately 5 million deaths worldwide. In addition, the total number of people with T2D worldwide is expected to increase to 642 million by 2040[2]. The greatest increase in the number of people with T2D will be in India. Moreover, the IDF estimates that ~50% of people with T2D are undiagnosed[2].

Recently, the Non-Communicable Diseases Risk Factor Collaboration (NCD-RisC) presented age adjusted global trends in T2D prevalence from 1980 till 2014, derived from 751 population studies involving approximately 4·4 million participants, aged 18 years and above[20]. Globally, the number of adults with T2D has shown a fourfold rise approximately, increasing from 108 million in 1980 to 422 million in 2014. Age-adjusted global T2D prevalence increased from 4.3% (95%CI 2.4 – 7.0) in men and 5.0% (95%CI 2.9 – 7.9) in women in 1980 to 9.0% (95%CI 7.2 – 11.1) and 7.9% (95%CI 6.4 – 9.7) in men and women respectively in 2014. South Asian countries accounted for a major proportion of global adult population with T2D (**figure 1.1**).

In the UK, almost 4 million people were diagnosed with T2D in 2015. The number of people with T2D in UK is expected to increase to ~5 million by 2025 with high rates among South Asians, the major immigrant population in UK[2].

Figure 1.1 Ten countries with the largest number of adults with T2D in 1980 and 2014.
Adapted from "Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants". The Lancet Volume 387, Issue 10027, April 2016.



1.5.2. Prevalence of T2D in South Asia

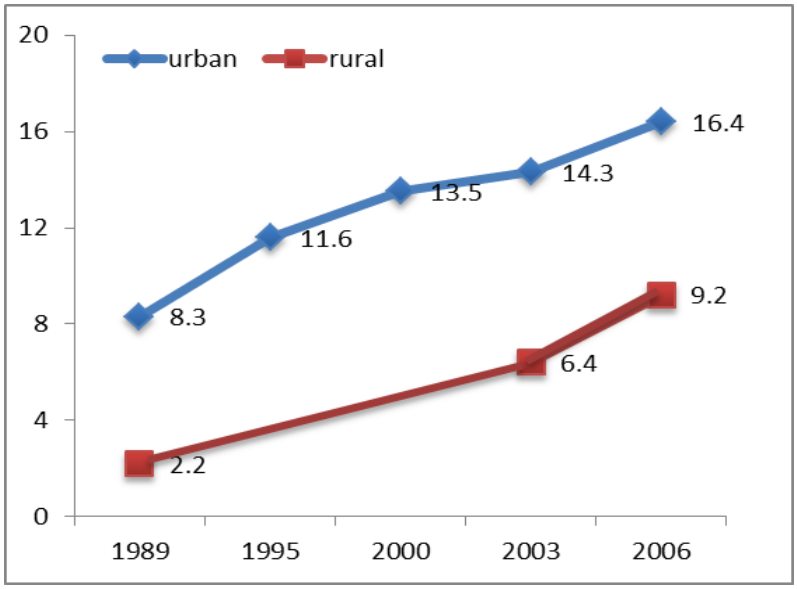
Approximately 75% of people with T2D are in low and middle income countries, of which India and China share the largest contribution. Worldwide there were an estimated 90 million South Asians with T2D in 2015, and this number is expected to increase to 140 million by 2040[2]. By this time South Asians will comprise the largest number of people with T2D worldwide.

Danaei et al. 2011[21], reported trends in the prevalence of T2D amongst South Asians. The prevalence of T2D increased from ~8% to ~11% amongst South Asians between 1980 and 2008 (**table 1.3**). Pakistani women showed the greatest increase where T2D prevalence doubled from 7.1% in 1980 to 14.1% in 2008. Population studies from the non-migrant South Asians show a marked urban-rural divide in T2D prevalence **(figure 1.2)**[22]. T2D affects ~15% of urban non-migrant South Asians, compared to ~5% of their rural counterparts **(table 1.4)**. In Sri Lanka, the prevalence of T2D is estimated to range from 9.9% to 19.6%[23,24]. Furthermore, the prevalence of IGT is high amongst non-migrant South Asians indicating a potential for further increase in the number of people with T2D[25-29].

Table 1.3 Prevalence of T2D amongst non-migrant South Asians in 2008. *Adapted from Danaei et al., 2011.*

Country	Prevalence of T2D (%)	
	Males	**Females**
India	11.1 (8.1 – 14.4)	10.8 (7.9 – 14.1)
Pakistan	11.7 (6.9 – 17.8)	14.1 (8.5 – 21.1)
Sri Lanka	9.3 (5.7 – 13.8)	8.6 (5.3 – 12.6)
Bangladesh	9.2 (4.9 – 14.8)	9.9 (5.5 – 15.6)

Figure 1.2 Temporal changes in the prevalence of type 2 Diabetes (T2D) amongst non-migrant urban and rural South Asians from 1989 till 2006.



These results are from population surveys conducted at Chennai, India in adults > 20 years

1989[20], 1995[23] – T2D prevalence surveys conducted in Chennai, India.

2000[188] – National Urban Diabetes survey (NUDS) in Chennai, India

2003[189] – Chennai Urban Rural Epidemiology study-17 (CURES-17)

2006[190] _ T2D prevalence in Chennai, India

Table 1.4 Prevalence (%) of type 2 diabetes (T2D) amongst urban and rural non-migrant South Asians. *Adapted from Jayewardene et al. BMC Public Health2012,12:380[19].*

Reference	Year	N	Age (yrs)	T2D (%)
India				
Ramachandran A et al[23]	1994-1995	2,183	≥ 20	Urban 11.6
Zargar AH et a[152]l	1996-1998	6,091	≥ 40	Urban 2.2; Rural 1.8
Singh RB et al[153]	1998	Urban 1,806; Rural 1,796	25-64	Urban 5.9; Rural 2.9
Sadikot et al[154] *(PODIS)*	1999-2002	Urban 10,617; Rural 7,746	≥ 25	Urban 5.9; Rural 2.7
Ramachandran A et al[161] *(NUDS)*	2000	11,216	≥ 20	Urban 13.9
Ajay VS et al[155]	2002-2003	10,930	20-69	Urban 10.1
Mohan V et al[156] *(CURES-17)*	2003-2004	2,350	≥ 20	Urban 15.5
Menon et al[157] *(ADEPS)*	2002-2005	986	>18	Urban 9
Mohan V et al[158]	2003-2005	Urban 15,239; Rural 13,524	15-64	Urban 7.3; Rural 3.1
Ebrahim S et al[159]	2005-2007	6,510	17-75	Urban 13.5; Rural 6.2
Ravikumar P et al[160]l *(CUDS)*	2008-2009	2,227	≥ 20	Urban 11.1
Bangladesh				
Sayeed et al[162]	1999-2000	4,923	≥ 20	Rural 3.8
Abu Sayeed et al[163]	2002	1,119	≥ 20	Rural 6.4
Sayeed et al[164]	2002-2003	5,265	≥ 20	Urban 10.5
Rahim MA et al[165]	2004	3,981	≥ 20	Semi-Urban 6.8
Hussain A et al[166]	2005	Urban 1555; Rural 4757	≥ 20	Urban 8.1; Rural 2.3
Rahman MM et al[167]	2004-2005	975	≥ 20	Rural 8.5
Hussain A et al[166]	2005	Urban 1555; Rural 4757	≥ 20	Urban 8.1; Rural 2.3
Rahman MM et al[167]	2004-2005	975	≥ 20	Rural 8.5
Pakistan				
Shera et al[168]	1995	967	≥ 25	Rural: Male 16.2; Female 11.6
Shera et al[169]	1999	1035	≥ 25	Rural: Male 9.2; Female 11.6
Shera et al[170]	1999	Urban 834 Rural 570	≥ 25	Urban: Male:11.1; Female:10.6 Rural: Male:10.3; Female:4.8
Basit A et al[171]	2002	2032	≥ 25	Rural 6.3
Srilanka				
Fernando et al[172]	1992-1993	633	30-74	Sub-Urban 5
Wijewardene et al[173]	2000-2001	6,047	30-65	Urban and rural 13.8
Katulanda et al[174] *(SLDCS)*	2005-2006	5,000	≥ 18	Urban 16.4; Rural 8.7

1.5.3. Prevalence of T2D amongst UK South Asians

There are approximately 9 million people of South Asian ancestry currently living in Europe and North America. In the UK, South Asians represent the largest ethnic minority group, comprising ~3 million people according to the 2011 census. The prevalence of T2D has been consistently reported to be higher amongst these migrant South Asians compared to native populations in all countries studied **(table 1.5)**. The reported prevalence of T2D among migrant South Asians ranges from ~10% in East Africa to ~34% in Singapore[28] [15,30-33,34-37].

In the UK, the prevalence of T2D amongst South Asians is reported to be up to 5 times higher than in the native European population. The Southall Diabetes Study, a large cross-sectional study of men and women in west London, concluded that prevalence of T2D was 3.8 times higher among UK South Asians than Europeans (19% vs. 4%)[38]. Recently, the Southall and Brent Revisited Study (SABRE) study, 20 year follow-up study of participants in the Southall study, reported that the prevalence of T2D was 22% amongst South Asians compared to 7% amongst Europeans[7]. The Health Survey of England (HSE) 2004[39] reported up to 4 times higher prevalence of T2D in South Asians compared to Europeans. According to the report, doctor-diagnosed T2D was 4 times more prevalent in Bangladeshi men and ~3 times more prevalent in Pakistani and Indian men compared with the European men. Amongst women T2D prevalence was highest in Pakistani women (5 times more common) followed by Bangladeshi (3 times more common) and Indian (2.5 times more common) women (**table 1.6**). Similar results have been reported by cross-sectional population studies in Birmingham[33] and Leicester[40].

Table 1.5 Prevalence (%) of type 2 diabetes (T2D) amongst migrant South Asians compared to the native population. *Adapted from Garduno-Diaz et al, 2012*[6].

Reference	**Setting** (Year)	**Study design**	**Sampling method**	**N** (male/female)	**Age** (Yrs)	**Diagnosis method**	**Prevalence of T2D (%)**
Dianna et al[155]	Mauritius (1987)	Population-based	Random	5,083	>20	OGTT	South Asians = 13.4 African = 12.3 Chinese = 13.2
McKeigue et al[11] **(Southall study)**	UK (1988-1991)	Cross-sectional	Work place, medical practices in west London	3696 (3145/551)	40-69	FGT/OGTT	South Asians = 19 Europeans = 4
Tan et al[156]	Singapore (1992)	Population-based	Random	3568 (1712/1856)	18-69	OGTT/FGT	South Asians 12.2 Malay = 10.1 Chinese = 7.8
Motala et al[157]	South Africa (1994)	Population cohort-10 year follow-up	Systematic cluster	563 (232/331)	>15	OGTT	South Asians = 16.2
Yeo et al[158]	Singapore (1984-1995)	Cross-sectional	Registry from previous surveys	5707 (2796/2911)	24-64	FGT	South Asians = 12.8 Malay = 4 Chinese = 3
Anand et al[27] **(SHARE)**	Canada (1996-1998)	Population-based	Stratified Random	985 (506/479)	35-75	FGT	South Asians = 10 Europeans = 5 Chinese = 2
Jenum et al[159]	Norway (2000)	Cross-sectional	Random	2513 (1101/1412)	30-67	Self-reported	South Asians: M= 14.3, F= 27.5 Natives: M= 5.9, F= 2.9[a]
Riste et al[160]	UK (2001)	Population-based	Random	1063 (517/546)	35-79	OGTT	South Asians = 33 Carribeans = 22 Europeans = 20
Hanif et al[161]	UK (2001-2003)	Cross-sectional	Random	435 (271/164)	20-75	OGTT	South Asians = 20 Europeans = NR[b]
Venkataraman et al[162]	United States (2004)	Community-based	Random	1046 (537/509)	17-87	Self-reported	South Asians = 18.3 Whites = NR
Dreyer et al[163]	UK (2006-2007)	Cross-sectional	Medical practices with deprived population	34359 (16637/17772)	>20	Diagnostic read code for T2D	South Asians = 11 Africans = 8 Europeans = 3.5
Dianna et al[155]	Mauritius (2009)	Population-based	Cluster	6371	>20	OGTT	South Asians = 21.9 Africans = 20.1 Chinese = 15.4
Tillin et al[32] **(SABRE)**	UK (2008-2012)	Population-based follow-up	Work place and medical practices in west London	4850 (3660/1198)	57-90	Medical records, FGT/OGTT, death certificates.	South Asians = 34 Europeans = 14

Table 1.6 Prevalence of self-reported, doctor-diagnosed T2D in England by minority ethnic group and sex, reported by the Health survey of England (2004).

	Prevalence of T2D (%)	
Ethnicity	**Males**	**Females**
Europeans	4.3	3.4
Indians	10.1	5.9
Bangladeshis	8.2	5.2
Pakistanis	7.3	8.6
Afrocarribeans	5.0	2.1
Chinese	3.8	3.3

1.5.4. Incidence of T2D amongst UK South Asians

The incidence of T2D has been reported recently amongst UK South Asian and European participants of the London Life Sciences Prospective Population study (LOLIPOP) study, a cross-sectional study of South Asians and Europeans in west London. Results from the study showed that 1608 (11·9%) of 13 535 South Asians and 306 (4·3%) of 7066 Europeans had incident T2D over a mean of 8·5 years (SD 1·8) of follow-up. South Asians who developed T2D during follow-up had higher baseline body mass index (BMI), waist circumference, waist-hip ratio, HbA_{1c}, Homeostatic model assessment-Insulin resistance (HOMA-IR, a measure of insulin ressitance), and fasting glucose and insulin concentrations than did South Asian controls (all p<0·0001). The age and sex adjusted risk of T2D was 3·1 times (95% CI 2·8–3·6; p<0·0001) higher amongst South Asians than Europeans. This risk difference remained 2·5 times (2·1–2·9; p<0·0001) higher even after adjustment for the major T2D risk factors. Similar results were also presented by the SABRE study which reported approximately 2.5-fold increased incidence of T2D amongst UK South Asians compared to Europeans[41].

1.5.5. Prevalence of undiagnosed T2D amongst South Asians

South Asians have a high prevalence of undiagnosed T2D. In the DECODA study[42] the proportion of previously undiagnosed T2D was highest in the youngest age-groups and lowest in the elderly. The proportion of undiagnosed T2D was slightly higher in women than in men at younger age groups.

The ADDITION-Leicester study[43] carried out a systematic screening program of 6,041 participants, aged 40–75 years for T2D. Results of the study demonstrated that the prevalence of undiagnosed T2D was 5.1% and 2.1% amongst South Asians

and Europeans respectively. Age and sex adjusted odds ratio for undiagnosed T2D was 2.30 (95% CI: 1.68 – 3.16, P<0.001) amongst South Asians compared to Europeans.

1.5.6. Insulin resistance amongst South Asians

The increased risk of T2D amongst South Asians is closely associated with the presence of insulin resistance and related metabolic disturbances[44]. Results from the LOLIPOP study, demonstrate an increase in fasting insulin and glucose, raised HOMA-IR, central adiposity, high triglycerides and low HDL cholesterol **(table 1.7)**. These results are consistent with the findings of other population studies comparing South Asians and Europeans, and identify insulin resistance as the major metabolic defect underlying the increased risk of T2D in UK South Asians[45].

The HOMA-IR is a method used to quantify insulin resistance, first described in 1985[46]. The original HOMA model was derived using data from physiological studies, describing glucose regulation as a feedback loop[47]. Because a feedback loop between the liver and beta-cells balances insulin secretion and hepatic glucose output, theoretically, it is possible to compute steady-state insulin and glucose concentrations. The original model was calibrated to give normal insulin resistance of 1. Higher insulin resistance is characterized by higher steady-state insulin levels. Insulin resistance can be determined from fasting glucose and insulin concentrations using the following formulas:

HOMA1-IR = (FPG x FPI)/22.5 (**mmol/l**)

OR

HOMA-IR = (FPG x FPI)/405 (**mg/dl**)

Although Hyperinsulinemic Euglycaemic Clamp remains the gold standard for assessing insulin resistance, it is not feasible for large studies, leaving HOMA-IR to be the preferred method for large scale research studies.

1.5.7. IGR and development of T2D

The risk for developing T2D is increased in individuals with IGR[48]. Edelstein SL et al[49], analysed 6 prospective studies. The results showed that T2D development in participants with IGT ranged from 23 to 62% within 2 to 27 years of follow up. The American Diabetes Prevention Program (DPP) also showed that ~10% of participants with IGT developed T2D per year[50]. Patients diagnosed with both IFG and IGT have a higher risk of developing T2D compared to patients with isolated IFG or IGT.

1.5.8. Prevalence of IGR amongst South Asians

The prevalence of IGR is consistently higher among South Asians compared to native populations. In the Newcastle Heart Project, the prevalence of IFG was 20% and 14% among South Asians and Europeans respectively[36]. The sub-group analysis showed highest rates of IGT amongst Pakistanis (24%). The Addition-Leicester study investigators reported higher frequency of IGR amongst South Asian individuals compared to Europeans (14.3% vs. 12.1%). Age and sex adjusted risk of IGR was ~60% higher in South Asians compared to Europeans (OR [95% CI]: 1.61 (1.33 – 1.93), $P<0.05$)[43]. Similarly, the DECODA study group showed that the age-specific prevalence of IGR was higher among South Asians than East Asians[42].

Table 1.7 Clinical characteristics of the London Life Sciences Population (LOLIPOP) study participants. Results are presented as mean (SD) and percentage (%) for continuous and categorical variables respectively. P value is for difference between South Asians and Europeans.

	South Asians	**Europeans**	**p-value**
N	**17,606**	**7,766**	
Age (years)	50.8 (11.2)	52.9 (11.5)	<0.001
Male (%)	61.2	59.6	0.017
Body mass index (kg/m2)	27.0 (5.3)	27.1 (4.7)	0.19
Waist hip ratio	0.95 (0.08)	0.92 (0.08)	<0.001
Glucose (mmol/L)	5.6 (1.6)	5.3 (1.2)	<0.001
Insulin (mU/L)	10.5 (9.9)	7.8 (8.2)	<0.001
HOMA-IR*	2.8 (3.5)	1.9 (2.4)	<0.001
Diabetes (%)	19.6	8.3	<0.001
Cholesterol (mmol/L)	5.2 (1.1)	5.4 (1.1)	<0.001
HDL cholesterol (mmol/L)	1.2 (0.3)	1.4 (0.4)	<0.001
LDL cholesterol (mmol/L)	3.2 (0.9)	3.3 (0.9)	<0.001
Triglycerides (mmol/L)	1.4 (1.0)	1.3 (0.9)	<0.001
Hypertension (%)	31.4	23.3	<0.001
Coronary Heart Disease (%)	10.5	5.6	<0.001

1.5.9. Morbidity and mortality of T2D amongst South Asians

Type 2 Diabetes presents ~10 years earlier amongst South Asians, increasing the life time exposure to hyperglycaemia and its complications[51]. The pattern of complications amongst South Asians differs from that in Europeans. South Asian patients with diabetes have higher rates of micro- and macro-vascular complications, particularly with respect to cardiovascular[52] and renal disease[4,53]. UK Prospective Diabetes Study (UKPDS) identified South Asian ethnicity as an independent risk factor associated with development of both albuminuria and renal insufficiency in T2D[54]. The Southall Diabetes Survey conducted an 11-year follow-up of 730 South Asians and 304 Europeans with established T2D[55]. The all-cause mortality rate ratio was 50% higher amongst South Asians compared to Europeans, at baseline. Participants aged 30-64 years at baseline had a mortality rate ratio of 1.80 (95% CI: 1.03 – 3.16, P<0.05) for circulatory deaths and 2.02 (95% CI: 1.04 – 3.92, P<0.05) for heart disease. Circulatory disease was responsible for 77% of South Asian deaths compared with 46% of European deaths. Amongst the survivors, history of myocardial infarction was 3.8 times (95% CI: 1.8 – 8.0, P=0.001) more likely to occur in South Asians than Europeans.

1.6. Pathogenesis of T2D

Type 2 Diabetes is a progressive disease in which increased insulin resistance typically precedes beta cell dysfunction[56]. The relative contribution of each varies from one population to another. High insulin resistance leads to IGR and overt *hyperglycaemia*. Insulin secretion is increased in the earlier stages of diabetes, causing *hyperinsulinaemia*. This is followed by a progressive reduction in pancreatic beta cell function causing relative deficiency of insulin and progression to clinical T2D[13].

1.6.1. Insulin resistance

Insulin resistance is a pathophysiological state in which body tissues have a reduced response to a given concentration of insulin, hence requiring higher-than-normal concentrations of insulin to maintain normal glucose levels. Insulin resistance has a strong genetic component. In addition, it is also influenced by obesity, diet composition and physical activity[57].

Recent studies have shown that, amongst various molecules involved in insulin-signaling cascade, dysfunction of the insulin receptor substrate (IRS)[58,59], the protein kinase B (PKB)[60], PI-3 kinase[61] and the forkhead transcription factor Foxo1a[62,63] play an important role in the development of insulin resistance.

The family of IRS proteins have a key role in the insulin-signaling cascade[59]. Studies have shown that serine phosphorylation of IRS proteins impairs the insulin-signaling cascade[64]. Studies with knockout mice show that IRS-1 and IRS-2 deficiency is associated with insulin resistance[58]. Homozygous IRS-1 gene defect in mice resulted in a mild form of insulin resistance[65,66]. Homozygous IRS-2 gene defect in mice, on the other hand, resulted in severe insulin resistance and pancreatic beta cell failure leading to T2D[58]. PKB has a role in activation and translocation of GLUT4 to the cell surface to transport glucose into the cell. Recent data from PKB2 isoform knockout animal models show insulin resistance, ending up with a phenotype closely resembling T2D in humans[67].

Recently, studies have revealed the possible role of PI3- kinase family[61], protein kinase C[68], PPARγ co-activator-1 (PGC-1)[69] and mitochondrial dysfunction[70] in the development of insulin resistance.

Adiposity is shown to be closely associated with insulin resistance and T2D. Patients with insulin resistance and T2D often have abnormal lipid metabolism and increased adiposity[71]. Studies have shown that high plasma fatty acids, in mice[72] and humans[73], disrupt insulin activation of IRS-1-associated PI3-kinase activity in skeletal muscle. In addition, high fatty acid levels have also been linked to GLUT4 translocation defects[74]. Adipose tissue also produces adipokines that regulate glucose homeostasis[75].

1.6.2. Pancreatic Beta-cell dysfunction and T2D

In T2D, there is a reduction in pancreatic beta-cell mass and function resulting in hyperglycaemia[76,77]. Autopsy findings from patients with T2D and IFG show a 63% and 40% reduction in pancreatic beta-cell mass respectively when compared to normoglycaemic individuals[77]. Results from the UKPDS demonstrated that pancreatic beta-cell dysfunction precedes the onset of hyperglycaemia by approximately 10 years and the beta cell function decreases progressively over time[78]. Possible mechanisms underlying pancreatic beta-cell dysfunction include: Genetic disposition[79], in utero malnutrition[80], glucotoxicity[81], lipotoxicity[82] and ectopic deposition of triglycerides in the pancreatic islets[83-85].

1.6.3. Mechanism of T2D in South Asians

Insulin resistance, rather than pancreatic beta-cell dysfunction, has been identified as the predominant mechanism underlying T2D amongst South Asians. Research studies demonstrate that South Asians have higher fasting insulin levels compared to other ethnic populations irrespective of age, sex or body mass index[86-89]. Moreover, South Asians have been reported to higher fasting insulin levels compared to Europeans even at birth[90], in school going children[91] and in teenagers[92]. Evidence

from studies using hyperglycaemic euglycaemic clamp show South Asian men and women of all ages have ~50% lower insulin sensitivity than their ethnic counterparts[93,94]. In addition, research studies show higher serum insulin levels after 2 hours and/or a higher insulin area under the curve with a normal glucose response, following an oral glucose tolerance test or meal tolerance test, in South Asians compared to other ethnicities[87,88,94]. Similar results have been reported following an insulin tolerance test[95].

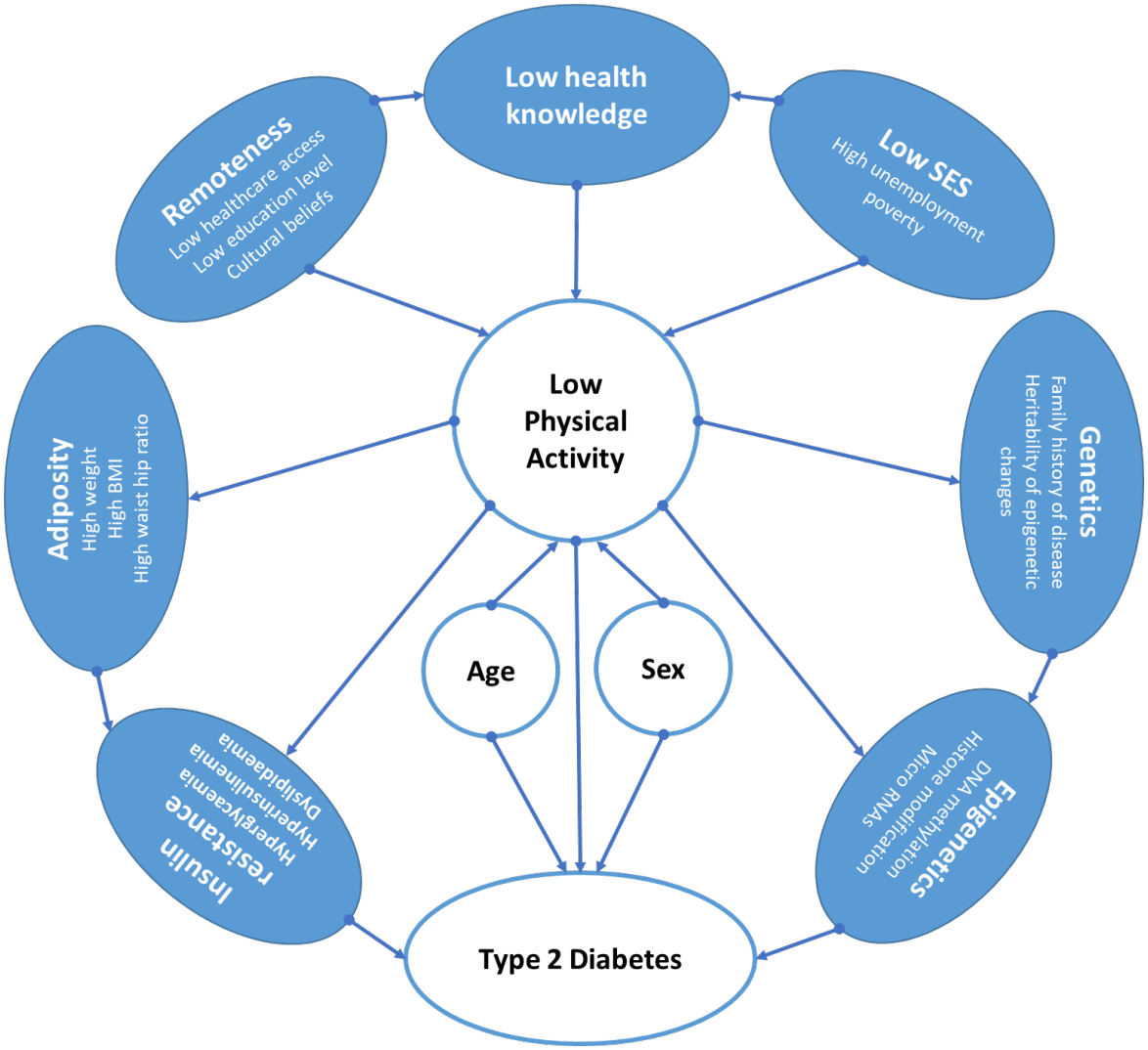
Pancreatic beta-cell function has been investigated in fewer studies compared with insulin resistance in South Asians. The UK Prospective Diabetes Study (UKPDS) was conducted on 5098 newly diagnosed T2D patients (82% Europeans, 10% South Asians, and 8% Afro-Caribbeans)[86]. Results of the study showed that pancreatic beta-cell function, measured with homoeostasis model assessment beta-cell function (HOMA-B), was best in South Asians whereas opposite was true for insulin sensitivity, measured with HOMA-S. Similar results were found by Snehalatha et al[96] where oral glucose tolerance test was performed in 289 South Asians with different stages of glucose tolerance. Results showed that insulin resistance was present in the early stages of glucose intolerance whereas IGT was not associated with a defect in insulin secretion. These results suggest that insulin resistance may precede beta-cell dysfunction in South Asians.

1.7. Risk factors for T2D

Type 2 diabetes is a complex multi-factorial disease driven by both genetic and environmental factors[97]. The major environmental risk factors underlying high T2D risk are obesity[98], unhealthy diet[99] and physical inactivity[100,101]. Picture below shows

conceptual framework that shows the complex interplay of lifestyle and genetic factors leading to the development of type 2 Diabetes.

The complex interplay of lifestyle and genetic factors leading to the development of type 2 Diabetes



1.7.1. Genetic factors

Genetic factors have a significant influence on T2D as evidenced from the twin and family studies[102]. High genetic concordance has been reported for T2D in monozygotic twins (0.29 to 1.00) compared to dizygotic twins (0.10–0.43)[103,104]. In family studies, siblings of a diabetic proband show ~4-fold increased risk for T2D in comparison with the general population (λ_S of 3.5 to 4)[104].

Genes associated with T2D were initially identified using the "linkage studies". This technique helped in identifying rare genetic variants having a strong effect (e.g. Maturity onset diabetes of the young) but was not very effective in identifying common genetic variants having a small effect, that underlie a large proportion of the risk of T2D.

Candidate gene association studies have also been conducted to find genetic variants associated with T2D. The candidate gene approach has identified some genetic variants (e.g. *PPARG, TCF7L2* and *KCNJ11*) associated with T2D[105,106]. But this approach has been less encouraging to identify the genetic contribution towards T2D.

Understanding of the genetic basis of T2D has been greatly progressed by Genome-wide association studies (GWAS). The first GWAS for T2D, published in 2007, confirmed the association of *TCF7L2* with T2D which was initially identified by the candidate-gene approach. The study also reported T2D associations for eight different genetic variants at five distinct loci[107]. This study was followed by GWAS from deCODE genetics[108], the Wellcome trust Case Control Consortium (WTCCC)[109], Diabetes Genetics Initiative (DGI)[110], and the Finland-US investigation of non-insulin

dependent diabetes mellitus genetics (FUSION)[111]. Following these studies, a meta-analysis of WTCCC, DGI and FUSION studies was carried out by the Diabetes and Genetics Replication and Meta-Analysis (DIAGRAM) consortium[112]. In 2010, The DIAGRAM consortium combined GWAS data from eight European cohorts (8130 T2D cases and 38,987 controls) and carried out the largest meta-analysis for T2D, called the DIAGRAM + meta-analysis. These landmark studies identified ~32 novel T2D associated loci[113].

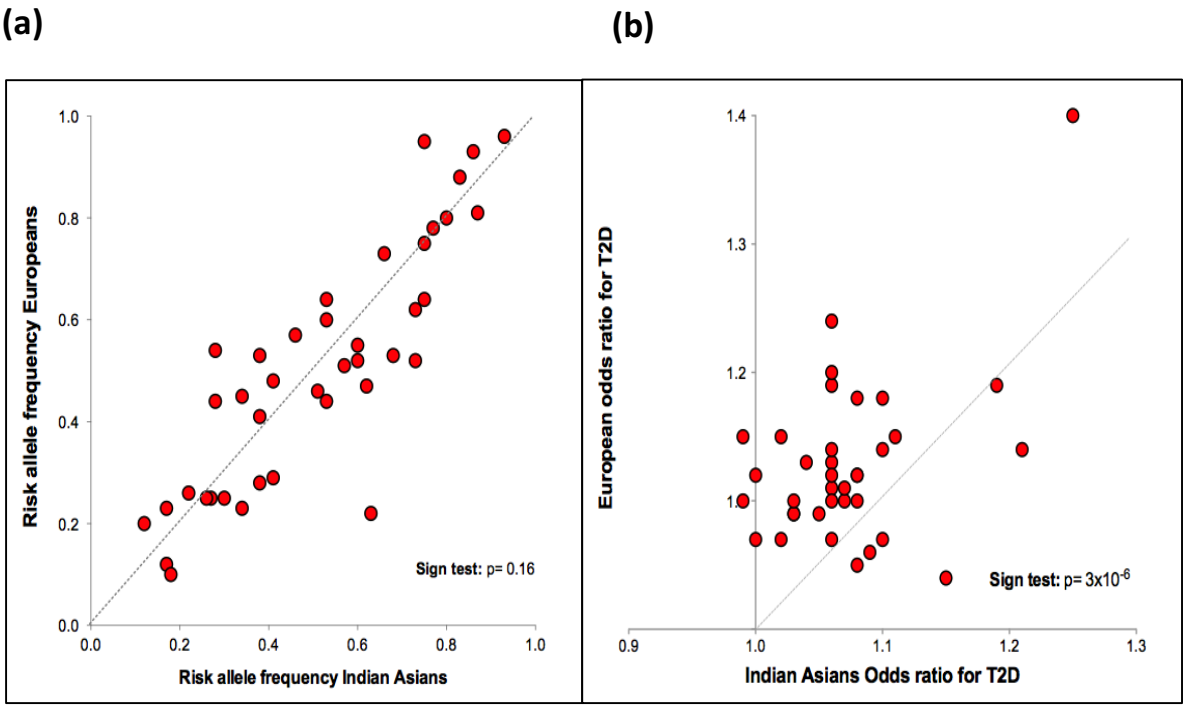
Recently, GWAS have been performed in South Asians. A GWAS was carried out by Kooner et al[114] in 5,561 T2D cases and 14,458 controls from the LOLIPOP study, Pakistan Risk Of Myocardial Infarction (PROMIS) study and Singapore Indian Eye (SINDI) study. The study identified T2D associated genetic variants at 6 novel loci (*GRB14, ST6GAL1, VPS26A, HMG20A, AP3S2* and *HNF4A*).

Another GWAS conducted amongst South Asians[115], including 6,738 T2D patients and 5,797 control subjects, identified a new T2D associated locus on the 2q21. Similarly, Saxena et al[116] discovered a previously unknown locus at 13q12 (*SGCG* gene) associated with T2D in a GWAS and a multi-stage meta-analysis carried on Punjabi Sikhs from Northern India.

The heritability of T2D amongst South Asians has not been investigated so far. However, studies in Europeans show that these known T2D genetic variants identified by GWAS explain only ~10% of the reported T2D heritability[112]. Furthermore, the genetic variants associated with T2D are shared amongst migrant South Asians and Europeans with no increase in effect size or risk allele frequency in the former[114]

(figure 1.3). The known genetic variants do not explain the increased T2D risk amongst South Asians compared to Europeans.

Figure 1.3 Results from the genome wide association study by Kooner et al[51]. (a) Comparison of risk allele frequencies of type 2 diabetes (T2D) genetic variants between South Asians and Europeans (b) Comparison of effect sizes/odds ratio (OR) of type 2 diabetes genetic variants between South Asians and Europeans



1.7.2. Obesity

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health. Obesity is usually defined by body mass index (BMI). A BMI of 18.5 kg/m^2 to 24.9 kg/m^2 is considered healthy for adults. Overweight is defined as a BMI between 25.0 kg/m^2 and 29.9 kg/m^2; and obesity is defined as a BMI of 30 kg/m^2 or higher. Other measures including waist circumference and waist-hip ratio have been used as indicators for body fat location and these measures may be better predictors of disease risk than the BMI[117].

Obesity is considered a major risk factor for insulin resistance and T2D[118]. Obesity plays an essential role in the development of T2D by mobilizing free fatty acids and inflammatory cytokines that promote insulin resistance[56].

High BMI levels are associated with an increased risk of T2D[119]. The risk of T2D development is increased by 2-8 fold at BMI 25 kg/m^2, 10-40 fold at BMI >30 kg/m^2 and >40 fold at BMI >35kg/m^2. However, this obesity associated increase in T2D risk is modified by various factors including age, sex, ethnicity, duration and distribution of adiposity[120,121].

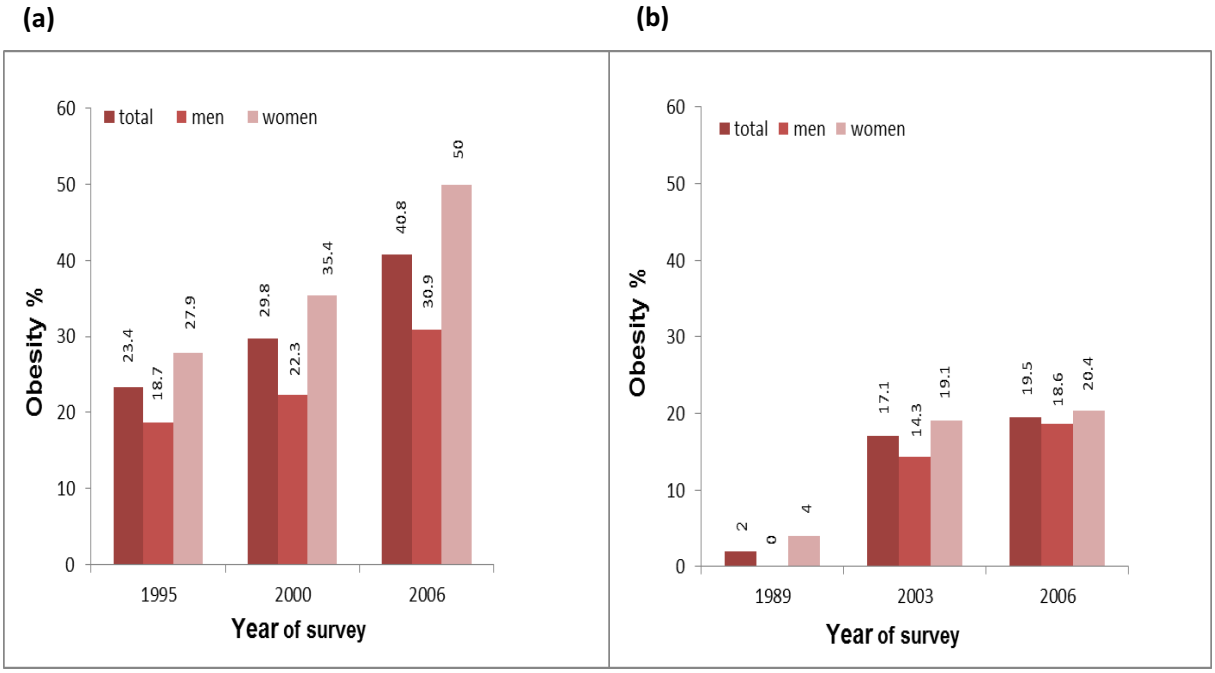
Results from interventional and prospective studies show that weight loss substantially reduces the risk of T2D[122,123]. Hamman et al[122] studied the contribution of weight loss towards reducing the T2D risk amongst participants of the Diabetes Prevention Program (DPP), USA. A reduction of 16% in T2D incidence was observed for each kilogram loss in weight. In the prospective Swedish Obese Subjects (SOS) study[123], obese patients undergoing gastric by-pass surgery and obese control subjects were followed for 8 years. Substantial weight loss was documented in the

gastric by-pass surgery group compared to the control group. This weight reduction in the gastric surgery group was associated with a reduced 8-year incidence of diabetes (odds ratio 0.16, 95% CI 0.07 to 0.36).

Recently, obesity has become one of the major health issues of the low and middle countries. The prevalence of obesity among South Asians has increased significantly over the past decade[124-126] (**figure 1.4)**. The prevalence of obesity is lower among the rural than in the urban population. However, rural population has shown a more rapid change over the past decade[127]. The prevalence of obesity is reported to be high amongst migrant South Asians compared to non-migrant South Asians.

Mean levels of BMI are similar amongst migrant South Asians and Europeans in the UK[128] **(figure 1.5),** suggesting that BMI does not identify or explain the increased risk of T2D in South Asians. In keeping with this, risk of T2D is higher amongst UK South Asians than Europeans (19% vs. 4%) at the same level of BMI[13]. Similar results were shown by the LOLIPOP study **(figure 1.6).** A meta-analysis of population based DECODE/A studies, reported a higher prevalence of T2D among both migrant and non-migrant South Asians starting at a lower BMI of 15-20 kg/m^2 compared to Europeans[129].

Figure 1.4 Temporal changes in prevalence (%) of obesity (BMI≥25 kg/m2) among urban and rural South Asians. (a) Shows the data for urban population. (b) Shows the data for rural population. *Adapted from Ramachandran et al. Journal of Obesity, 2010*[65]



These results are from population surveys conducted at Chennai, India in adults > 20 years

1989[20]*, 1995*[23] *– T2D prevalence surveys conducted in Chennai, India.*

2000[188] *– National Urban Diabetes survey (NUDS) in Chennai, India*

2003[189] *– Chennai Urban Rural Epidemiology study-17 (CURES-17)*

2006[190] *T2D prevalence in Chennai, India*

Figure 1.5 Proportion (%) of Europeans and South Asians (Indians, Pakistanis and Bangladeshis) having a body mass index (BMI) value of =/>30kg/m2.

Source: Health Survey for England 2004 report (The Health of Minority Ethnic Groups).

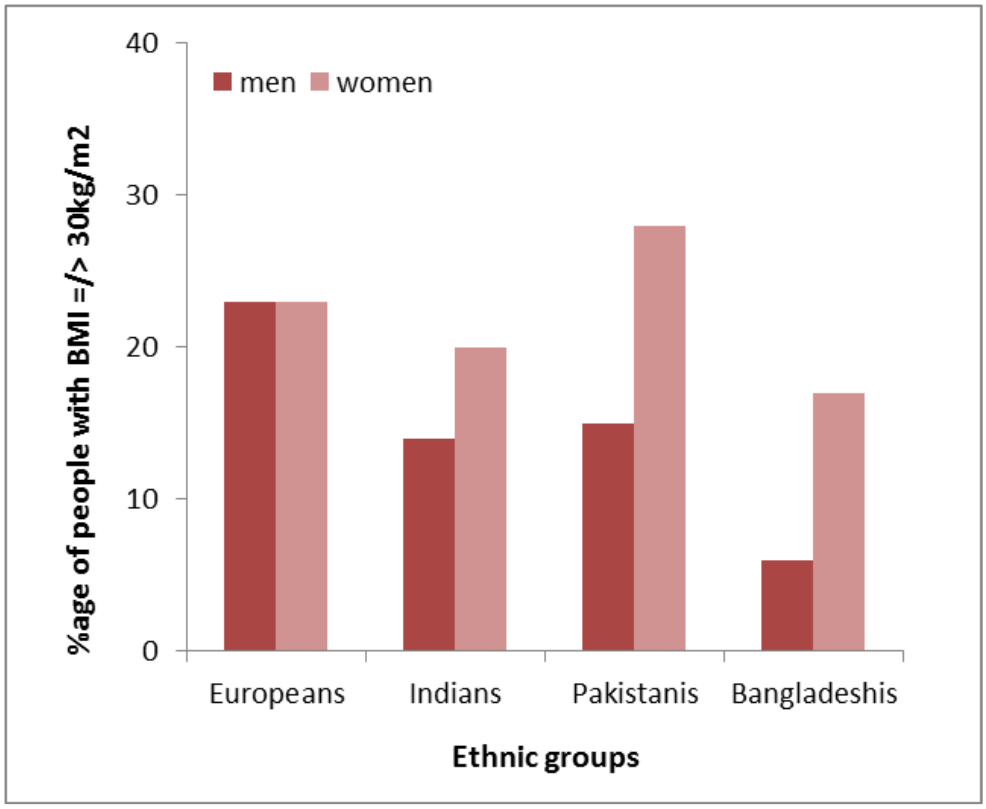
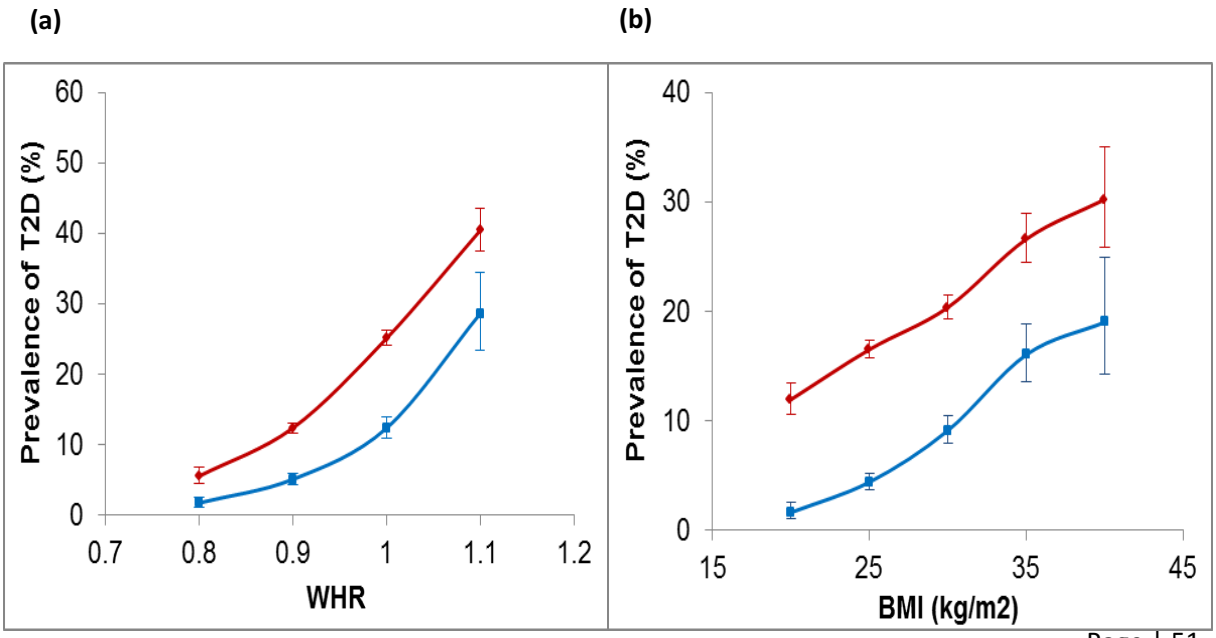


Figure 1.6 Prevalence (%) of type-2 diabetes (T2D) amongst South Asians (in red) and Europeans (in blue) at a given (a) body-mass index (BMI) and (b) waist-hip ratio (WHR).



Central adiposity (accumulation of excessive visceral and sub-cutaneous fat) is more common amongst migrant South Asians than Europeans[130-132], and has been proposed to account for the increased risk of T2D amongst South Asians[131,133]. However, recent data suggest that central adiposity also does not explain the excess T2D risk amongst migrant South Asians compared to Europeans. The LOLIPOP study has reported a 3.6 times higher risk of T2D among UK South Asians than Europeans. After adjustment for WHR, waist circumference and BMI the risk of T2D in UK South Asians remained up to 3 times higher compared to Europeans[134]. Recent results from the SABRE study also showed that controlling for central obesity did not abolish the South Asian-European difference in T2D incidence[41] . In multivariate regression analysis the central obesity and insulin resistance explained two fold excess in T2D prevalence amongst South Asian women but did not account for the excess T2D prevalence among men[41].

1.7.3. Dietary factors

Unhealthy diet has been identified as an important determinant of T2D[135]. The diet composition is most commonly determined by using “weighed 7 day diaries” and “food frequency questionnaires”.

Studies that have used more robust procedures like Doubly labelled water for measuring energy expenditure or urinary nitrogen for measuring protein intake, show food diaries and questionnaires to be less accurate[136]. These methods have several limitations that include a change in eating behaviour when individuals are asked to record their intake (*observation effect*) and mis-reporting or usually under reporting the eating behaviour, more likely to occur with increasing age and weight (*reporting effect*). In addition, most of the diet composition tools are based on chemical

analysis done long time ago and are poor representative of South Asian foods and thus may be less accurate for capturing recent dietary habits[137].

Diet high in total fat contributes in the development of T2D and related metabolic disturbances including obesity, insulin resistance and poor lipid profile[138]. Research studies show that animal fat is associated with a greater risk of T2D compared with vegetable fat. The San Luis Valley Diabetes study[139] followed subjects for 3 years. Results of the study showed that fat consumption in subjects who developed T2D was 43.4% of total energy intake compared to 40.6% and 38.9% in those who had IGT and reverted to normal glucose tolerance respectively. Recently however, studies report that specific fat type, instead of total fat, is associated with development of T2D[140-142].

Results from the Nurses' Health Study[143] demonstrated that high vegetable and poly-unsaturated fat (PUFA) are associated with reduced risk of T2D. Data from prospective studies indicate that ω-6 PUFAs have beneficial effect on insulin sensitivity and reduce the risk of T2D development[144-146]. However prospective cohort studies did not demonstrate a relationship between long chain ω-3 PUFAs and T2D[139]. Diet high in mono-unsaturated fatty acids (MUFA) have shown beneficial effects in T2D[147,148], but their role is still inconclusive[143].

Saturated fatty acids are reported to be positively associated with hyperglycaemia and glucose intolerance by both cross sectional and prospective studies[149,150]. Results from large cohort studies also show an association between saturated fatty acids and incidence of T2D. The KANWU study[148] compared diets rich in saturated fatty acids with those rich in MUFAs. Results showed that consumption of

saturated fatty acids is associated with ~10% decrease in insulin sensitivity while no change was observed with diet rich in MUFAs.

Trans-fatty acids (TFA) are formed by partial hydrogenation of fish or vegetable oils. The Nurses Health Study[74] reported ~30% increased relative risk of T2D with diets rich in TFAs. A diet intervention study by Riserus et al[75] also confirmed that diet rich in trans-fatty acids is associated with the development of T2D.

High carbohydrate intake may cause hyperinsulinemia, high plasma triglyceride levels and low HDL-cholesterol levels. However, epidemiologic studies conclude that neither total carbohydrates nor simple sugars (e.g. sucrose) predict the risk of T2D development[151]. Prospective and intervention studies consistently report a reduction in the incidence of T2D with high fibre diets, even after adjustment for confounding factors[152,153].

Data from cross-sectional studies show a positive association of high protein intake with insulin resistance and glucose intolerance[154]. Prospective studies also show that the incidence of T2D increases with high protein intake[155,156]. In contrast, intervention studies demonstrate an improvement in glycaemic control in parallel to weight loss with high protein intake[157,158].

Recommended dietary nutrient intake: According to the dietary recommendations 45-65% of total energy intake should be from carbohydrates, 20-30% from fat and 10-35% from protein, with a maximum of 25% of total energy from added sugars[159].

Dietary pattern amongst South Asians: South Asians living in the US have been show to get 8% of energy intake from saturated fatty acids[160]. In India, mean saturated fatty acid intake is 6.5%, however no association was shown between saturated fatty acid intake and T2D risk[161]. The Southall study assessed the relationship of hyperinsulinaemia to dietary intake (7-day weighed intake) among South Asians and Europeans. Results from the study revealed that dietary intake of South Asians contained lower total fat, higher ω-6 PUFAs, higher starch content, lower ω-3 PUFAs and similar sucrose content as compared to Europeans[128]. Adjustment for the different diet components could not explain the insulin resistance difference amongst the migrant South Asians and Europeans. Migration and acculturation[162] to the host country has resulted in substitution of the traditional South Asian diet with the western less healthy high fat diet. Despite these changes in the diet of migrant South Asians, their dietary intake is closer to recommended calorie intake compared to that of European counterparts hence does not explain the increased risk of T2D among migrant South Asians.

1.7.4. Physical activity

Physical activity is defined as “any/all bodily movements” produced by skeletal muscles resulting in energy expenditure. *Exercise* is a subset of leisure time physical activity and involves planned, structured and repetitive body movements performed to improve or maintain one or more components of physical fitness. In contrast, *physical fitness* is defined as "the ability to carry out daily tasks with vigour and alertness, without undue fatigue and with ample energy to enjoy leisure-time pursuits and to meet unforeseen emergencies".

1.7.4.1. Dimensions and Domains of Physical Activity

The four main dimensions of physical activity include: (i) frequency – 'the number of events of physical activity during a specified time, (ii) duration – time spent in performing a particular activity during a specified time frame, (iii) intensity – the physiological effort associated with performing a particular type of activity. Intensity indicates the metabolic demand of an activity. It can be objectively quantified with physiological measures (e.g. oxygen consumption, heart rate, respiratory exchange ratio), subjectively assessed by perceptual characteristics (e.g. rating of perceived exertion, walk-and-talk test), or quantified by body movement (e.g. stepping rate, 3-dimensional body accelerations) and (iv) type of activity. These dimensions of physical activity are fundamental because their assessments provide the ability to calculate physical activity energy expenditure.

Physical activity is commonly classified into four main domains: (i) occupational (paid or unpaid work related), (ii) Domestic (household work, yard work, physically active child care, chores), (iii) Transportation (walking/bicycling to or from place to place) (iv) Leisure-time (discretionary or recreational activities like sports, hobbies, exercise, volunteer work).

1.7.4.2. Quantification/units of physical activity

Basal metabolic rate (BMR) is the minimal rate of energy expenditure per unit time to keep the body functioning at rest[163]. In healthy normal-weight individuals at rest, the body oxygen consumption is ~3.5 ml/kg per min which equals 1*kcal/kg/h* (1litre of O2 consumption = 5 kcal). BMR is typically measured after a full night's sleep in a laboratory under optimal fasting conditions in a physically and psychologically undisturbed state, in a thermally neutral environment.

BMR accounts for about 60 to 75% of the daily energy expenditure by individuals. BMR depends on metabolically active lean body tissue; mainly muscle (although all tissues make some contribution). Body weight is, therefore, an important factor in determining BMR. Other important determinants include age and sex. After the age of 20, BMR typically declines by 1–2% per decade, mostly due to loss of fat-free mass,[164] although there is a high variability between individuals[165]. The proportion of body weight as fat is higher amongst women compared to men, contributing towards the lower BMR of a woman than a man of the same body weight. Several equations have been developed to predict BMR. Historically, the most notable one was the *Harris-Benedict equation*, which was created in 1919.

It may not always be possible to determine BMR under strictly controlled conditions. When the conditions are not completely controlled, the resultant measurement of energy expenditure is called the *resting metabolic rate* (RMR). For practical purposes, RMR is sometimes considered approximately equivalent to the BMR.

The *metabolic equivalent* (MET) is a common unit used to express exercise intensity. MET is defined as the ratio of energy expenditure during a specific physical activity to the resting energy expenditure (RMR). 1 MET is equal to the rate of oxygen consumption at rest (3.5ml/kg/min). MET can be thought of as an indicator of the intensity of activities: for example, an activity with a MET value of 4, such as brisk walking would require three times the energy that an average person consumes at rest (e.g., sitting quietly). MET is often used to express the intensity and energy expenditure of physical activities in a way comparable amongst individuals of different weight. Actual energy expenditure (e.g., in calories or joules) during an activity

depends on an individual's weight; therefore, the energy expenditure of the same activity will be different for individuals of different weight. However, since the RMR is dependent on the weight as well, it is assumed that ratio of physical activity energy expenditure to the resting energy expenditure (RMR) will remain more or less stable for the specific activity and thus independent of each individual's weight.

The *Compendium of Physical Activities* was developed for use in epidemiologic studies to standardize the assignment of MET intensities in physical activity questionnaires. The compendium was published in 1993[166] and updated in 2000[167] and 2011[168]. Research studies have been using the compendium to assign intensity units to assess energy expenditure in physical activity studies. Based on the associated METs, physical activities are classified as (i) low intensity (<3 METs), (ii) moderate intensity (3 - 6 METs) and (iii) vigorous intensity (>6 METs). Common physical activities and their assigned MET values are enlisted in **table 1.8.**

Table 1.8 Metabolic Equivalent (MET) values for commonly performed physical activities, from the Compendium of Physical Activities.

Physical activity	**MET**
Light intensity activities	**< 3**
Sleeping	0.9
watching television	1
writing, desk work, typing	1.5
walking, 1.7 mph (2.7 km/h), level ground, strolling, very slow	2.3
walking, 2.5 mph (4 km/h)	2.9
Moderate intensity activities	**3 to 6**
bicycling, stationary, 50 watts, very light effort	3
walking 3.0 mph (4.8 km/h)	3.3
calisthenics, home exercise, light or moderate effort, general	3.5
walking 3.4 mph (5.5 km/h)	3.6
bicycling, <10 mph (16 km/h), leisure, to work or for pleasure	4
bicycling, stationary, 100 watts, light effort	5.5
Vigorous intensity activities	**> 6**
jogging, general	7
calisthenics (e.g. pushups, situps, pullups, jumping jacks), heavy, vigorous effort	8
running jogging, in place	8
rope jumping	10

Physical activity level (PAL) is defined as the total energy expenditure (TEE) in a 24-hour period, divided by the basal metabolic rate (BMR), for a non-pregnant, non-lactating adult[169].

PAL=TEE per 24 hours/BMR

BMR is determined by age, sex, body size and body composition. Dividing TEE by BMR adjusts for these individual specific characteristics. A larger subject has higher BMR than a smaller subject. TEE is higher as well, and divided by BMR might result in a comparable PAL to a smaller subject. Based on the PAL, physical activities can be classified as: (i) Extremely inactive (<1.40), (ii) sedentary and light activity (1.40-1.69), (iii) Moderate activity (1.70-1.99), (iv) Vigorous activity (2.00-2.40) and (v) Extremely active (>2.40) (**table 1.9**).

Table 1.9 Classification of lifestyles according to physical activity intensities based on the Physical Activity Level (PAL).

Lifestyle	Example	PAL
Extremely inactive	Cerebral Palsy patient	<1.40
Sedentary	Office worker getting little or no exercise	1.40-1.69
Moderately active	Construction worker or person running one hour daily	1.70-1.99
Vigorously active	Agricultural worker (non-mechanized) or person swimming two hours daily	2.00-2.40
Extremely active	Competitive cyclist	>2.40

1.7.4.3. Physical activity guidelines

In 2007, the American College of Sports Medicine (ACSM) and American Heart Association (AHA) published, *"Physical Activity and the Public Health: Updated Recommendations for Adults*". This report states that: healthy adults should perform moderate intensity aerobic physical activity, for a minimum of 30 minutes' duration, on 5 days per week or vigorous intensity aerobic exercise, for a minimum of 20 minutes, on 3 days per week. Recommendations can be met by combining moderate and vigorous intensity exercise. This recommended amount of moderate or vigorous intensity aerobic activity is in addition to daily life light intensity activities, such as casual walking, grocery shopping, taking out the bins or activities less than 10 minutes in duration. In addition, the guidelines state that 8 to 10 exercises should be performed at least twice each week using the major muscle groups that maintain or increase muscular strength and endurance. A weight should be used to maximise strength development.

A comprehensive report, *"Physical Activity Guidelines Advisory Committee Report*", was published by the US Department of Health and Human Services (USDHHS) in 2008. This evidence based report was used by WHO to create the 2008 'Global Recommendations on Physical Activity for Health'.

The guidelines by USDHHS state that to gain substantial health benefits, adults should do at least 150 minutes of moderate intensity, or 75 minutes of vigorous intensity aerobic physical activity per week, or an equivalent combination of moderate and vigorous intensity aerobic activity. This aerobic activity should be performed in episodes of at least 10 minutes, and preferably, it should be spread throughout the week. Additional health benefits are gained by engaging in physical activity beyond

this amount. Adults should also do muscle-strengthening activities that are of moderate or vigorous intensity and involve all major muscle groups on two or more days a week, as these activities provide additional health benefits.

According to the Advisory Committee report, the ACSM guidelines are too specific. Existing scientific research does not show any evidence of whether the health benefits of 30 minutes on 5 days a week are any different from the health benefits of 50 minutes on 3 days a week. The report states that adults will benefit from exceeding the minimum recommended amounts of physical activity because of the dose response relation between physical activity and health. The report also suggests that adults who participate in any amount of physical activity gain some health benefits.

All the physical activity guidelines' reports also provide detailed recommendations for targeted populations that include children and adolescents, adults, older adults, pregnancy and post-partum, adults with disabilities, adults with medical conditions, and weight loss and maintenance.

Step based recommendations: A common guideline used by many organisations is the number of steps per day an individual should take. Although step based recommendations from around the world vary, 10,000 steps/day is generally used as a reasonable target for healthy adults.

1.7.4.4. Physical activity and T2D

Inadequate physical activity has been recognised as one of the leading risk factors for global mortality contributing to approximately 3.2 million deaths each year[170]. The association of low physical activity levels with increased risk of T2D is

well established. A meta-analysis of cross-sectional **(table 1.10)** and prospective **(table 1.11)** studies carried out by Jeon et al[85] reported ~30% risk reduction of T2D in the physically active group compared to those who were sedentary. Results from lifestyle intervention studies show that increased physical activity reduces the risk of developing T2D by almost 58% ($p<0.001$)[50,171]. The DPP USA investigated the role of metformin and lifestyle intervention in reducing T2D incidence in a sample of 3234 non-diabetic individuals with raised fasting and postprandial glucose levels. Participants were directed to perform at least 150min/week of moderate intensity physical activity. There was a reduction of 58% (95%CI, 48-66%) and 31% (95%CI, 17-43%) in the incidence of T2D in the lifestyle intervention and metformin group respectively[50]. Similar findings were reported by The Finnish Diabetes Prevention Study (DPS)[171]. The Da Qing Study in China showed that risk of T2D was lowered by 46% ($p<0.005$), 42% ($p<0.005$) and 31% ($p<0.03$) in response to exercise, exercise plus diet and diet interventions respectively[172].

Table 1.10 Cross-sectional studies of physical activity and the risk of type 2 diabetes. *Adapted from Jeon et al. Diabetes Care 2007[85].*

Reference	Age (yrs)	*N*/*n* cases	Diabetes assessment	Moderate-intensity activity	OR (95% CI)	Adjustments
James et al[164], 1998 (U.S.)	30–55	916/78	Type 2 diabetes: FBG or use of antidiabetes medication	Walking for ≥15 min at a time or home maintenance/gardening vs. inactive	0.51 (0.20–1.28)	Age, sex, education, BMI, waist-to-hip ratio
Baan et al[165], 1999 (Netherlands)	55–75 (males)	503/69	Type 2 diabetes: 2-h postload glucose or use of antidiabetes medication	Walking (≥285 vs.<60min/week)	1.45 (0.63–3.32)	Age, BMI, waist-to-hip ratio, family h/o diabetes, smoking
				Bicycling (yes vs. no)	0.26 (0.14–0.49)	
				Gardening (yes vs. no)	0.56 (0.29–1.06)	
	55–75 (females)	513/49	Same as male participants	Walking (≥270 vs. <45 min/week)	1.05 (0.47–2.36)	
				Bicycling (yes vs. no)	0.37 (0.18–0.78)	
				Gardening (yes vs. no)	0.46(0.21–1.01)	
Defay et al[166], 2001 **(POLA study)** (France)	>60 (males)	1,113/213	Type 2 diabetes: FBG or use of antidiabetes medication	Usual intensity of household activities (moderate vs. light)	0.67 (0.48–0.94)	None
	>60 (females)	1,419/132	Same as male participants	Usual intensity of household activities (moderate vs. light)	0.61 (0.40–0.95)	None
van Dam et al[167], 2002 **(Zutphen Elderly study)** (Netherlands)	69–89	424/90	IGT or newly detected type 2 diabetes: OGTT	Taking walks (>20 min/day vs. none)	0.92(0.46–1.88)	Age, other physical activities
				Bicycling (>20 min/day vs. none)	0.37(0.20–0.70)	
				Gardening (>20 min/day vs. none)	0.33(0.16–0.66)	
Combe et al[168], 2004 (France)	20–74	3,759/299	Newly detected type 2 diabetes: FBG	Walking >1 h/day (yes vs. no)	0.81(0.64–1.04)	None
Dunstan et al[169], 2004 (Australia)	≥25 (males)	8,299/1,555	IFG, IGT, or newly detected type 2 diabetes: OGTT	Walking and "other" moderate-intensity activities (≥2.5 vs. <2.5 h/week)	0.96 (0.66–1.40)	Age, sex, education, family h/o diabetes, smoking, dietary factors, TV watching, waist.
	≥25 (females)		Same as male participants	Walking and "other" moderate-intensity activities (≥2.5 vs. <2.5 h/week)	0.73 (0.53-1.01)	

Table 1.11 Prospective-cohort studies of physical activity and the risk of type 2 Diabetes (T2D). *Adapted from Jeon et al. Diabetes Care 2007[85].*

Reference	Country	Age (yrs)	*N*/*n* cases	Moderate-intensity activity	Diabetes assessment	Follow-up (yrs)	Results
Helmrich et al[170], 1991	U.S.	39–68	5,990/202	Non-vigorous (~5 MET h) sports only vs. no sports participation; walking: ≥15 vs. <5 blocks/day	Self-report of physician diagnosis	14	*RR = 0.76
Lynch et al[171], 1996	Finland	42–60	897/46	Activities requiring <5.5 MET h for at least 2 h/week (yes vs. no)	OGTT/on anti-diabetes medicine	4.2	**OR = 0.44
Hu FB et al[172], 1999	U.S.	40–65	70,912/1,419	Walking in MET h/week among those who did not perform vigorous activities (highest vs. lowest quintile)	Self-report of physician diagnosis (validated)	8	RR (least to most quintiles of PA): without BMI adjustment = 1.0, 0.77, 0.75, 0.62, 0.54; with BMI adjustment = 1.0, 0.84, 0.87, 0.77, 0.74
Folsom et al[173], 2000	U.S.	55–69	34,257/1,997	Frequency of activities ≤6.0 MET h (>4 times/week vs. rare or never)	Self-report of physician diagnosis	12	RR = 0.69
Okada et al[174], 2000	Japan	35–60	6,013/444	Weekend LTPA vs. being sedentary on weekends	OGTT	10	RR : moderate intensity = 0.75 Vigorous intensity = 0.55
Wannameth ee et al[175], 2000	U.K.	40–59	5,159/196	Regular walking or recreational activities vs. sedentary	Primary care records	16.9	RR = 0.66-0.69
Hu FB et al[176], 2001	U.S.	40–75	37,918/1,058	Walking in MET h/week (highest vs. lowest quintile)	Self-report of physician diagnosis (validated)	10	RR (least to most quintiles of PA) = 1.00, 0.78, 0.65, 0.58, and 0.51
Hu G et al[177], 2003	Finland	35–64	14,290/373	LTPA (walking, cycling, light gardening) >4 h/week vs. less	National registries	12	*** HR (associated with light, moderate and vigorous PA) = 1.00, 0.70 and 0.74
Weinstein et al[178], 2004	U.S.	≥45	37,878/1,361	Walking (≥4 h/week vs. none)	Self-report of physician diagnosis (validated)	6.9	HR (compared with the least active first quartile): second quartile = 0.91; third quartile = 0.86; fourth quartile = 0.82.
Hsia et al[179], 2005	U.S.	Post-menopausal	87,907/2,271	Walking (highest vs. lowest quintile)	Self-report of anti-diabetes medication	5.1	HR (least to highest PA quintiles): walking = 1.00, 0.85, 0.87, 0.75, 0.74 Total PA= 1.00, 0.88, 0.74, 0.80, 0.67

PA- physical activity, LTPA- leisure time physical activity; *RR = Relative Risk (of developing type 2 Diabetes)
**OR = Odds Ratio (odds of developing T2D); ***HR = Hazard Ratio (hazard of T2D development)

Based on these data, WHO recommends at least 150 min/week of moderate intensity (3-6 METS) aerobic physical activity or 75 min/week of vigorous intensity (>6 METS) aerobic physical activity or an equivalent combination of moderate and vigorous intensity aerobic physical activity[173]. However, approximately 60% of the adult global population fails to achieve this minimum physical activity recommendations[173].

1.7.4.5. Mechanisms underlying the relationship of physical activity with T2D

Physical activity has both short and long term effects that reduce the incidence of T2D[174]. The primary mechanism for this is improvement in insulin sensitivity[175-178]. In the European Relationship between Insulin Sensitivity and Cardiovascular Risk (RISC) Study, increased insulin sensitivity was positively associated with physical activity ($p<0.001$) and negatively associated with sedentary time[179]. An inverse association of physical activity with fasting insulin levels was also reported by The Cross Cultural Activity Participation Study conducted in USA. Results of the study demonstrated a decrease of 6.6% ($p<0.05$) in fasting insulin levels for an increase of 30 minutes of moderate intensity physical activity[180]. Ekelund et al[181] investigated the effect of physical activity on metabolic parameters. After adjusting for fat mass, a reduction of 5.3% was observed in the fasting insulin levels with physical activity, along with an improvement in the post prandial glucose levels. The improvement in insulin sensitivity may be mediated by both adiposity-dependent and adiposity-independent mechanisms.

Improvement in insulin sensitivity through weight loss: Physical activity plays an important role in reducing obesity[182,183], the major cause of insulin resistance. The

role of weight loss in improving insulin sensitivity is well established[184,185]. A weight loss of 12% is associated with an improvement of 30-40% in the fasting insulin levels and ~60% improvement in insulin sensitivity[186]. High levels of physical activity are known to help in the reduction and maintenance of weight by increasing the energy expenditure of the human body[182,183] even in the absence of diet restriction[187]. The physical activity level recommended for promoting weight loss is 60 minutes per day of moderate intensity physical activity on majority days of the week (twice the normal physical activity levels recommended by WHO) which is associated with ~2100kcal of energy expenditure per week[188,189]. Intervention studies have reported a weight loss of ~12% in individuals with high physical activity levels (60min/day) compared to ~1% in the low physical activity group[177]. Thus, increased physical activity levels can help reduce obesity related T2D by promoting weight loss.

Improvement in insulin sensitivity independent of weight loss: Increasing physical activity levels have been shown to provide protection against insulin resistance and T2D even in the absence of reduced fat mass[181,190]. Results from a study comparing the association of physical activity and insulin sensitivity between Pima Indians (overweight) and Mauritians (lean) showed that increased physical activity levels are inversely related to serum insulin concentration irrespective of the BMI suggesting an independent effect of physical activity on Insulin sensitivity without any influence on body composition[191].

Increased physical activity is associated with an increase in glucose transporter 4 (GLUT4) in the muscle cells. The acute effects of physical activity occur primarily by increasing GLUT4 translocation in the muscle cells through insulin-dependent[192] and insulin-independent pathways. Studies in the insulin receptor

knockout mice[193] showed an increased glucose uptake in response to high physical activity levels compared to the control group confirming the significance of insulin independent glucose uptake mechanisms. Moreover, increased physical activity also has lasting effects on GLUT4 concentration in the muscle cells[194]. A study conducted on Wistar rats[195] showed increased concentration of GLUT4 in muscle cells after 6 weeks of exercise while there was no change in the GLUT4 concentration after 1 day or 1 week of exercise. These exercise-induced chronic effects on GLUT4 are suggested to occur primarily by an increase in transcription factors involved in GLUT4 gene expression leading to increased intra-cellular GLUT4 stores[194]. Because of the increase in GLUT4 levels (due to immediate and delayed effects of increased physical activity) there is increased uptake of blood glucose by the muscle cells and reduced insulin resistance.

In addition to the primary effects of increased physical activity on insulin sensitivity the secondary effects of increased physical activity in preventing insulin resistance and T2D include (i) improved lipid profile[196] and (ii) reduction of systolic blood pressure[197] thus reducing the clustering of metabolic risk factors associated with Insulin resistance and T2D[198].

1.7.4.6. Contribution of physical inactivity to T2D among South Asians

According to Health survey of England 2008, only 39% men and 29% women meet physical activity recommendation in England[112]. While physical activity levels do not meet the recommendations among both Europeans and South Asians, South Asians show even lower levels of physical activity than their ethnic counterparts[11,12,199]. **Table 1.12** summarises the reported levels of physical activity amongst South Asians compared to Europeans.

Table 1.12 Physical activity levels amongst South Asians and Europeans. Adapted from Babakus and Thompson International Journal of Behavioural Nutrition and Physical Activity 2012[180].

Reference	Year	Sample size		Design	PA* measure	Main findings
		South Asians	Europeans			
Mc Keigue et al[181].	1992	2648	1751	cross-sectional	self-report	Age-adjusted mean *PA (MJ/week): **SA: 3.0, European: 4.2
Williams et al[182].	1994	173		cross-sectional	self-report	% reporting ever taking vigorous PA: Males: SA = 46%, Europeans = 59% Females: SA = 38% Europeans = 44%
Lip et al[183].	1996	84 (female)	72 (female)	cross-sectional	self-report of regular exercise	Lower proportion of exercisers among South Asians
Pomerleau et al[116].	1999	291 (female)	246 (female)	cross-sectional	self-report	SA women walked least for transport compared to European and Afro-Caribbean: 22% vs. 44% and 40%, respectively. 1% of SA women participated in sport and none cycled
Riste et al[160].	2001	132	471	cross-sectional	self-report: validated questionnaire, physical activity over past week	% physically active defined as 3X20min/week (95% CI): Pakistani men = 6.8%(0-13); Pakistani women = 5.2%(0-11) European men = 37.8%(23-53); European women = 29.4%(13-46)
Lean et al[184].	2001	119	140	cross-sectional	self-report	18% of Migrant SA performed sport and exercise 30% of British-born SA performed sport and exercise
Ye et al[185].	2009	1,651	74,424	cross-sectional	self-report	% reporting physical inactivity(unadjusted): Europeans = 37.2%, SA = 41.8%, Other Asian = 41.0%
Yates et al[186].	2010	1164	4310	cross-sectional	self-report: IPAQ*** short form	% in PA level category: European men: Low = 22%, Moderate = 28%,High = 50%, SA men: Low = 37%, Moderate = 25%, High = 38%, European women: Low = 27%, Moderate = 33%, High = 32%, SA women: Low = 40%, Moderate = 28%, High = 32%
Williams et al[114].	2010	2120	13,293	observational-longitudnal	self-report: 4 week recall	% reporting no weekly physical activity(unadjusted): Europeans = 28.1, Indian = 37.1, Pakistani/Bangladeshi = 56.7.
Williams et al[187].	2010	1130	818	cross-sectional	self-report: based on IPAQ	% reporting more than 3 hours sedentary/day: SA = 45.6, Europeans = 47.5, % reporting some PA: SA = 73.2%, Europeans = 79.4%

*PA- physical activity, **SA- South Asians, *** IPAQ- international physical activity questionnaire.

Williams et al[200] used data from Health Survey of England 1999-2004 to investigate physical activity behaviour and coronary heart disease among migrant South Asians and Europeans. The proportion of migrant South Asian and European population who met the recommended physical activity levels was 28.1% and 47.0% respectively. A study by Hayes et al[201] compared physical activity levels of migrant Indians, Pakistanis, Bangladeshis and Europeans using a Physical Activity Index ranging from 0-8. Results from the study showed that proportion of people who met physical activity recommended guidelines among Europeans, Indians, Bangladeshis and Pakistanis was 48, 29, 12 and 13% respectively. Similarly, Pomerleau et al[202] showed that the proportion of women who walked at least 2.5 km/day in their leisure time was 22% and 44% amongst migrant South Asians and Europeans respectively. Reasons underlying low physical activity levels amongst South Asians may include lack of awareness, social and cultural barriers, religion, lack of facilities, economic status, time constraints and health issues.

The potential beneficial effects of physical activity in preventing T2D have been investigated in South Asians. The Indian Diabetes Prevention Program (IDPP)[203] investigated the role of lifestyle modification (diet + physical activity) and metformin in prevention of T2D amongst South Asians with impaired glucose tolerance. The relative risk reductions for lifestyle modification and metformin group were 28.5 and 26.4% respectively and there were no combined benefits. These results suggest that physical activity is as effective in the prevention of T2D amongst South Asians as is medical treatment and therefore physical activity can provide an efficient and cost effective mean for reducing and delaying the risk of T2D development amongst South Asians.

1.7.4.7. Measurement of Physical Activity

The ability to accurately measure Physical activity energy expenditure is of increasing interest due to growing evidence that physical activity plays an important role in preventing and controlling many health problems especially T2D and associated complications such as CVD.

The available methods used for measuring physical activity are presented in **table 1.13**. The Doubly Labelled Water, Room Calorimetry and Indirect Calorimetry are the most accurate methods, and are considered the gold standards. However, these are of limited use in population studies because they are expensive, and require specialized equipment and expertise[204]. As a result, most epidemiological studies quantify physical activity through the use of questionnaires. Advantages of questionnaires include low cost, ready adaptation to a variety of settings/populations and ease of use. However, accuracy and reproducibility are low. As a result, there has been increasing interest in the development of devices for measurement of physical activity in large scale population studies. Physical activity measurement devices should be objective, accurate, reproducible, low cost, acceptable to study participants and require minimal expertise. Several devices have been developed. Pedometers measure physical activity by counting steps. These are inexpensive and readily available but do not measure the intensity, duration or frequency of physical activity[204]. Other improved electronic devices include accelerometers and heart rate monitors[205]. These monitors are low to moderate in cost and give a better estimation of Physical activity energy expenditure[204,205]. Global Positioning System monitors and multi-location devices have also been used but their validity is still being assessed[204].

Table 1.13 Advantages and disadvantages of various subjective and objective methods used for measuring physical activity.

METHOD	ADVANTAGES	LIMITATIONS
Subjective methods -Diaries -Interviews -Questionnaires	Inexpensive Easy to administer Can be used in large populations Can capture qualitative and quantitative information	Low validity Low reliability Subjective bias Only provide a rough estimate of Energy expenditure.
Direct observation	Accurate recording of PA type Contextual information Applicable to children and adults	Time consuming Potential reactivity of study participant (Hawthorne effect) Cannot be done for longer periods and daily PA monitoring Subjectivity of the observer
Pedometers	Low cost Easily available Measures footfalls	Captures walking or running only Cannot measure Intensity, duration or frequency of physical activity. Cannot measure activities like weight lifting and biking
Accelerometers [uniaxial/triaxial]	Low to moderate in cost Easy to use Objectively measure physical activity Measures the intensity, duration and frequency of physical activity can be used for large population studies and long term daily free-living PA monitoring	Cannot measure biking, weight lifting and water related activities Energy equations have been developed for specific activites, so cannot estimate other activities accurately
Accelrometers + HR monitors	Higher accuracy than simple accelerometers Objectively measure physical activity Measures the intensity, duration and frequency of physical activity	Higher cost than accelerometers Poor participant compliance due to placement of the electrodes Results may be confounded by stress, anxiety, fever and caffiene that affect the heart rate
Calorimerty **-Room** **-Indirect**	High accuracy.	Expensive Mostly not suitable for monitoring outside the laboratory setting Not feasible for large population studies
Doubly labelled water	Accurate as compared to other methods. Gold standard for measuring physical activity energy expenditure. Does not change daily PA behaviour.	High cost Requirement of specialized instrument and expertise Measures energy only over a long period of time Cannot specify activity pattern Not appropriate for large population studies
Global positioning system [gps] monitors/ multi location devices	Validity and reliability is still being assessed.	Limited validity and reliability. Only work outdoors Uncomfortable for long term monitoring Measures activities with true translational motion only.

Accelerometers

Accelerometers are currently the most commonly used electronic sensors for measuring physical activity objectively[206-210]. These devices provide an objective measure of intensity and frequency of wide range of physical activities in a specified period of time[211]. Hence, measurements from accelerometers are superior to subjective methods (diaries, self-reports, questionnaires)[212] as well as pedometers[204]. Accelerometers differ in size, sensitivity, cost, storage memory and energy expenditure calculation. However, they are mostly small, portable and can be worn on wrist, waist or ankle.

Accelerometers operate by measuring acceleration (g) of moving body[211,213] along a given axis or multiple axes at the same time, using technologies like piezo–electric, micro–mechanical springs, and changes in capacitance[214]. Accelerometers convert raw acceleration into electrical signals called "counts" that are proportional to the muscular force producing motion[215]. Counts is a metric which is specific for each brand of device[211]. These counts are summed over a specified time period (epoch) and stored. Physical activity energy expenditure is calculated by the accelerometers using customised equations[205,209-211,216,217] that convert counts into Metabolic Equivalents (METS) and calories/joules. Many accelerometers have the storage capacity of up to 21 days using a 60 second epoch.

Accelerometers have been reported to produce accurate and reproducible data in both laboratory[218-220] and free-living settings[210,216] and have become the standard device for measuring physical activity objectively. Nonetheless; these devices have a number of limitations[221]. Accelerometers only measure the dynamic acceleration, underestimate the energy expended during non-ambulatory activities or

activities where the weight is partially supported e.g. weight lifting, heavy digging, cycling, ice skating and these physical activity measuring monitors are not worn during water related activities[221]. Measurement of physical activity is also affected by the position of monitor on the body[222,223] and the recording period[224,225].

1.7.4.8. Limitations of current knowledge regarding physical activity and T2D in South Asians

Almost all published studies investigating physical activity levels amongst South Asians have used physical activity questionnaires **(Table 1.12)**, an approach known to be of limited accuracy and confounded by reporting bias[226]. The questionnaires used have all been developed in the English language, and are focussed on physical activities common in European population. None of the questionnaires used for measuring physical activity levels have been validated for use amongst South Asians.

In one of the studies[227], pedometer has been used to document physical activity levels amongst South Asians. Pedometers are inaccurate measures of energy expenditure because they only capture footfalls without recording the intensity, frequency or type of physical activity[204].

Accelerometers are well validated tools for measurement of energy expenditure in European populations[228]. However, the validity of these physical activity measuring devices amongst South Asians is unknown. Body habitus is known to influence the accuracy of accelerometers[229]. Given the well documented anthropometric differences between South Asian and European populations[7,13], accelerometers cannot be assumed to function equally well in the two populations.

Finally, all previous studies of physical activity and T2D amongst South Asians are cross-sectional. The lack of longitudinal and interventional studies to investigate physical activity levels and T2D risk amongst South Asians introduces the potential for confounding and limits causal inferences.

Future studies should focus on improved and accurate methods for quantification of physical activity amongst South Asians and should consider longitudinal and interventional designs to determine the relation between physical activity and T2D amongst South Asians. This will help in a better understanding of the role of low physical activity levels in excess T2D burden and developing effective interventions to prevent T2D in this high risk ethnic group.

1.8. Aims and objectives

The *general aim* of my thesis is to investigate the contribution of low physical activity to the increased risk of T2D in UK South Asians compared to Europeans.

My *objectives* are to:

1. Evaluate three commercially available devices for objective measurement of physical activity by accelerometery (Actiheart, Actigraph GT3X+ and Geneactiv) in UK South Asians and Europeans, to identify the device which most accurately quantifies physical activity in the two populations.

2. Quantify physical activity levels among South Asian and European men and women in the UK using the objective measurement device selected above (1). Use the data to determine whether physical activity levels differ between the populations, and to validate and calibrate the physical activity questionnaire.

3. Additionally use the data generated above (2) to examine the relationships of objectively measured physical activity with insulin resistance and related metabolic disturbances that predict T2D, amongst South Asians and Europeans.

4. Examine the relationship of physical activity with incident T2D amongst the 27,000 South Asian and European men and women participating in the ongoing LOLIPOP study.

Chapter 2: Methods and materials

2.1. Introduction

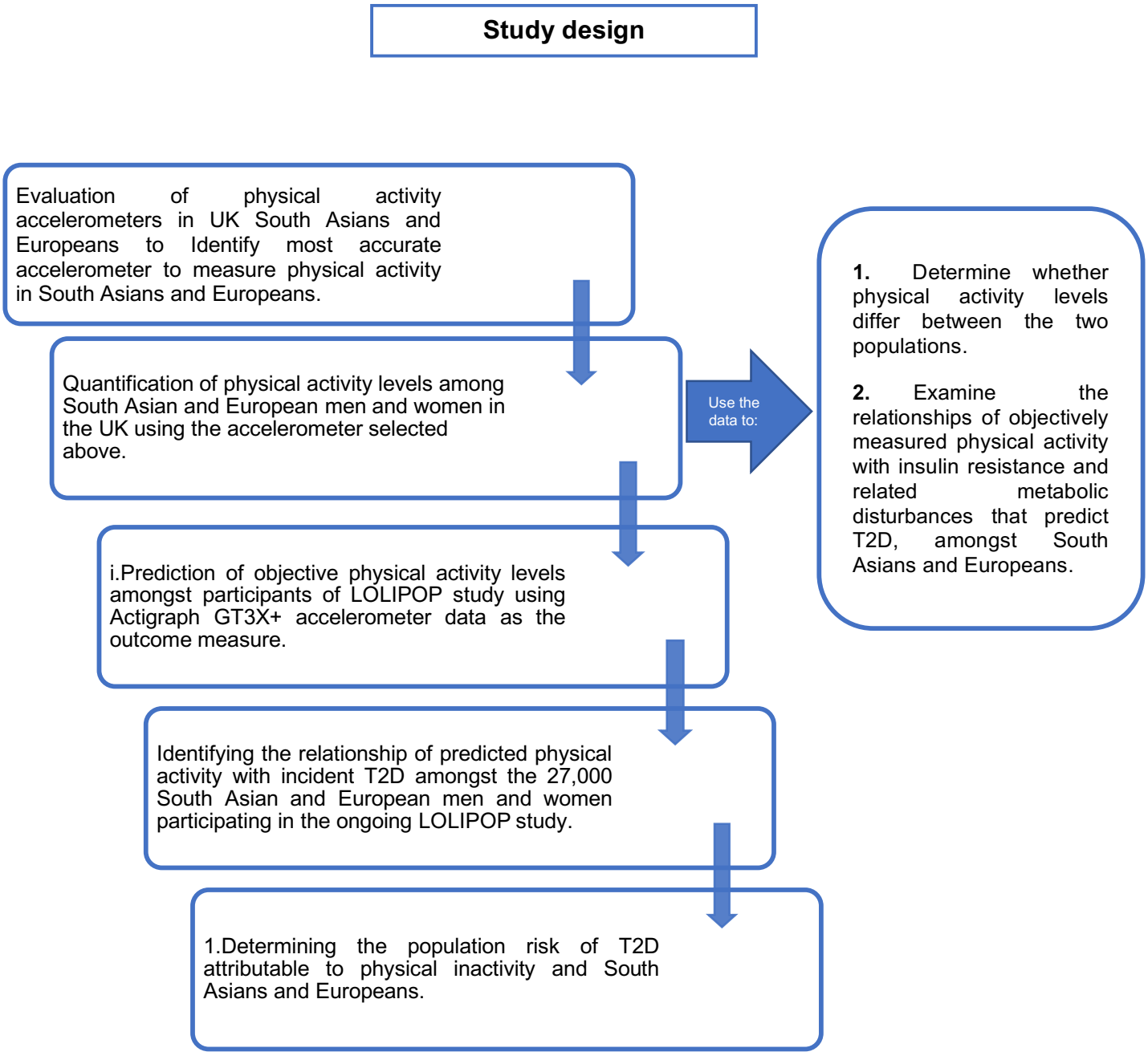
I performed cross-sectional and prospective population studies to investigate the efficacy of physical activity measuring tools in South Asians compared to Europeans and determine the contribution of physical activity levels to the increased risk of T2D amongst South Asians compared to Europeans.

My research study and accompanying protocol has been approved by a Research Ethic Committee. All subjects gave written informed consent to participate in the research projects.

This chapter describes the methods used for recruitment and characterisation of participants and the biochemical tests performed, and the approaches to statistical analyses.

2.2. Design

My thesis consists of both cross-sectional and prospective study designs as shown below.



2.2.1. Objective 1

I performed a cross-sectional study for validating three commercially available accelerometers amongst South Asians and Europeans from patients who were being referred for an Exercise Treadmill Test (ETT), in the presence of a trained physiologist and a senior cardiology registrar. I completed a brief questionnaire regarding medical and personal history and carried out all the physical measurements and positioned the accelerometers on the participants prior to the placement of ECG leads and blood pressure cuff.

The research study was approved by the research ethics committee and written informed consent was given by all the participants.

2.2.2. Objectives 2 and 3

I collected cross-sectional data from amongst the participants of the LOLIPOP study, an ongoing prospective population study in west London, to examine the relationships of physical activity with insulin resistance and related metabolic disturbances that predict T2D, amongst South Asians and Europeans. The LOLIPOP study is described in detail under **section 2.2.3.**

Data was collected regarding personal and medical history through an interviewer administered questionnaire. Physical and biochemical assessment of the participants was carried out. Insulin resistance was measured by Homeostasis model of insulin resistance (HOMA-IR) using the published formula: *HOMA-IR= (glucose*insulin)/22.5*. Data was analysed using multivariate regression analysis models with adjustment for various confounding factors.

2.2.3. Objective 4

I investigated the association of physical activity with new-onset T2D among the UK South Asians and Europeans in the prospective LOLIPOP study. These participants from LOLIPOP study have provided follow-up consent for incident metabolic events as well as for storage of blood for future biochemical and genetic studies.

Participants of the LOLIPOP study at Ealing Hospital have provided information about their daily physical activity levels by completing leisure-time physical activity questionnaires (LPAQ). They are undergoing clinical follow-up to identify and validate the presence of new-onset T2D. Consenting participants attend a 45 minute appointment, where they are asked to provide information regarding any significant medical event, and have physical and biochemical measurements taken. This has enabled reassessment of biochemical cardiovascular risk factors and new onset T2D.

A team of trained research nurses and laboratory technicians facilitated data collection for the LOLIPOP study, under the supervision of research fellows and principal investigators. Roles of the team members included: making appointments for study participants, undertaking a standardised and structured assessment of metabolic and cardiovascular risk factors, anthropometric measurements, recording 12-lead ECGs, collecting blood samples via venepuncture for biochemical and genetic analyses and entering the collected data into research database. A two-month structured training program was provided to each member of staff before they started to work independently. Each member of staff was revalidated at 3 monthly intervals and record was maintained in the training manual.

The LOLIPOP study has been approved by a Research Ethics Committee. All participants gave written informed consent.

2.3. Study participants

2.3.1. Objective 1

I recruited 62 South Asian and 40 European men and women, aged 25 to 75 years, from amongst patients undertaking an ETT for clinical indications at Ealing Hospital NHS Trust, London, United Kingdom. Participants were excluded if they had any absolute or relative contraindication to exercise testing as per the ACSM guidelines for exercise testing and prescription, 2010. Participants who stopped before 3 minutes (stage 1) of the ETT or had any mobility issues affecting their performance on the treadmill were also excluded.

Written information was sent to the patient by post before the appointment. A clear explanation of the procedure, along with its benefits and possible risks, was given just before the ETT as well and a written informed consent was obtained. Any mobility issues that might affect the ability of the participants to perform on the ETT were assessed.

The test was conducted in the presence of a trained physiologist and a cardiology registrar in a fully equipped setting.

2.3.2. Objectives 2 and 3

I recruited a total of 902 South Asian and European men and women, aged 35-75 years, from the LOLIPOP study. In addition to the routine physical and biochemical measurements, physical activity levels were measured objectively

amongst these participants using physical activity accelerometer. Physical activity in these participants was also measured using LPAQ.

2.3.3. Objective 4

I investigated 16,774 South Asian and 7,031 European men and women of the LOLIPOP study to determine the association of physical activity with new-onset T2D. LOLIPOP study is a prospective population based cohort study involving South Asian and European men and women, aged 35-75 years. Participants for the study have been recruited from lists of 58 General Practitioners based in West London, United Kingdom. Recruitment of participants was started in 2001 and baseline data collection was completed in 2008. South Asian ethnicity was identified as having all four grandparents born on the Indian subcontinent (India, Pakistan, Sri Lanka and Bangladesh). European ethnicity was identified as having all four grandparents born in Europe.

2.4. Participant characterization

2.4.1. Objective 1

Data was collected regarding personal, behavioural, family and medical history through an interviewer-administered questionnaire. Physical measurements included height, weight, waist circumference and hip circumference. Height was recorded to the nearest 0.1cm using a stadiometer, mounted on a hard, flat surface. Weight was recorded to the nearest 0.1kg. Waist and hip measurements were recorded to the nearest 0.1cm using a non–stretchable measuring tape. Waist circumference was defined as the minimum circumference between iliac crest and lowest rib. Hip circumference was defined as the maximum circumference over the greater trochanters and buttocks. (The questionnaire and physical measurements

have been discussed in detail in the following sections). No biochemical measurements were taken.

2.4.2. Objectives 2, 3 and 4

2.4.2.1. Clinical questionnaire

Data regarding past medical and surgical history, family history, current prescribed medications, social history, alcohol and smoking habits and metabolic and cardiovascular risk factors was collected using a standardized interviewer-administered questionnaire. In addition, data on place of birth, birthplace of all four grandparents, mother tongue, religion, and years resident in the UK were recorded for each participant.

2.4.2.2. Physical assessment

Physical measurements included height, weight, waist and hip circumference, and blood pressure.

Height

Height was measured to the nearest 0.1cm using a stadiometer, mounted on a hard, flat surface. Participants did not wear any turbans, hats or shoes during the measurement. Participants stood with their back against the height rule, with both feet together and head, buttocks and heels touching the wall. They were asked to look straight ahead, and the stadiometer bar moved down to touch the top of the head, pressing the hair flat.

Weight

Weight was recorded to the nearest 0.1kg, using digital scales mounted on a hard, flat surface. The patient was weighed after an overnight fast, wearing light clothing only.

Waist-Hip Ratio

Waist-hip ratio (WHR) was measured after an overnight fast wearing light clothing only, standing straight with feet together. Measurements were made to the nearest 0.1cm using a non-stretchable measuring tape, applied around the body without twists, and gently touching skin, without compressing soft tissue. Waist circumference was defined as the minimum circumference at a point midway between iliac crest and lowest rib. Hip circumference was defined as the maximum circumference over the greater trochanters and buttocks.

Blood Pressure

Blood pressure was measured using an OMRON 705 CP blood pressure monitor. Sitting blood pressure was measured in the right arm, after 10 minutes' rest, in loose clothing, and in a warm room. The cuff was positioned in level with heart, over the brachial artery and the lower edge of the cuff 2-3 cm above the antecubital fossa.

2.4.2.3. Biochemical Measurements

Sample collection

Standard venepuncture technique was used to collect venous blood samples. Venepuncture was performed with the patient lying on a couch for at least 10 minutes, at the antecubital fossa. A tourniquet was applied gently around the upper

arm and released once the vein had been cannulated. Samples were collected into pre-labelled vacuum filled sample tubes, with additive where appropriate. Once filled, the sample tubes were gently inverted 2-3 times.

Routine biochemistry

Blood was taken for fasting glucose, fasting insulin lipid profile, fasting urea and electrolytes and HbA1c. Blood samples were analysed in the Clinical Chemistry laboratories at Ealing Hospital NHS Trust, London, UK. The samples were analysed using commercially available assays summarised in **table 2.1**. Whole blood was additionally collected and stored at -80^{o}C for future genetic testing. HOMA-IR was calculated using the formula: HOMA-IR = fasting glucose*fasting insulin/22.5.

Table 2.1 Methods used for biochemical analysis.

	Method	Analyser
Glucose	Enzymatic, colorimetric method	Roche/ Hitachi cobas c 501
Insulin	Sandwich principle	Cobas e 411
Cholesterol	Enzymatic reference method with hexokinase	Roche/ Hitachi cobas c 501
Triglycerides	Enzymatic colorimetric test	Roche/ Hitachi cobas c 501
HDL-C	Homogeneous enzymatic colorimetric test	Roche/ Hitachi cobas c 501
HbA1c	High performance liquid chromatography	Bio-Rad VARIANTTM II TURBO

2.5. Exercise treadmill test

Participants completed a graded exercise treadmill test with 12-lead ECG and blood pressure monitoring. A baseline ECG and blood pressure reading was recorded at rest. All the devices were worn by the patient on the described position (**section 2.7.4**) before starting the test. The test began gently and gradually the level of exercise intensity was increased through a combination of increased treadmill speed and incline. The speed and incline of the treadmill increased at 3 minute intervals according to the standard Bruce protocol. ECG was recorded throughout and blood pressure measured intermittently during the ETT. The test was concluded according to clinical indications that include: development of chest pain, presence of ST elevation, ST depression (2 mm or more), arrhythmias, hypotension or if the patient became tired and was unable to continue. In addition, elevation of blood pressure to dangerous levels such as >250/115 mm Hg also led to termination of the test.

Actual energy expenditure (METs) was derived by exercise testing software (GE Cardiac Assessment System for Exercise Testing 8000) based on the speed and grade of the stage completed on the Bruce protocol. The equation for Metabolic Equivalents follows: METs = speed x 26.8 x (0.1 + 1.8 x grade/100) + 3.5/3.5, where grade is given in percent and speed is given in miles per hour. MET levels are extrapolated between stages of exercise. Two minutes of a stage must be completed to obtain full stage MET values. At any point thereafter, full credit is given for the stage.

The Equation used to calculate METs from the ETT is not predicted by the individual's body composition (weight, waist and hip circumference). Therefore, the performance of this equation is similar in different ethnic groups despite the differences in their body compositions.

2.6. Leisure-time physical activity questionnaire (LPAQ)

Participants were asked to recall the activity they performed for at least 10 minutes continuously during leisure time, in the last seven days. Results are presented as the estimation of PAEE in MET.minutes/week and the time (minutes) spent in each physical activity category. MET.minutes/week of specific activity is computed by multiplying MET value of particular intensity activity with minutes spent in that activity, as described in the data analysis guidance notes of the physical activity questionnaire. Physical activities are classified as light, moderate or vigorous according to the classification scheme of CDC (USA). Study participants were asked to quantify the frequency and duration of time spent (minutes) in moderate (3-6 METs, e.g. aerobics, brisk walking, cycling, football, jogging, swimming, skipping, tennis) and vigorous activities (>6 METs, e.g. circuit training, fast swimming, high impact aerobics, mountain biking, running, squash, skiing) during leisure time in the previous week. The total time (in minutes) spent in leisure time physical activity was calculated, and converted to MET.minutes (MET.minutes). LPAQ was completed by all LOLIPOP study participants at baseline as well as follow-up.

2.7. Physical activity accelerometers

I investigated three commercially available accelerometers amongst South Asians and Europeans:

i. Actigraph GT3X+

ii. Geneactiv and

iii. Actiheart

The Actigraph GT3X+ and Geneactiv are tri-axial accelerometers. Actiheart is a chest worn monitor that records both accelerometery and heart rate to estimate physical activity.

2.7.1. Actigraph GT3X+

The Actigraph GT3X+ (Actigraph, Pensacola, FL), is a tri-axial accelerometer that measures and records time varying accelerations, ranging in magnitude from ± 6*g.* The Actigraph GT3X+ accelerometer, in conjunction with the ActiLife software application, delivers objective, accurate physical activity and sleep measurements including raw acceleration, activity counts and vector magnitude, energy expenditure, steps taken, physical activity intensity, body position, amount of sleep and sedentary time. Raw acceleration from each axis is stored in memory for future analysis. This raw acceleration can be analysed directly or further processed by the recommended software. Technical specifications of the Actigraph GT3X+ accelerometer is presented in **table 2.2**.

Table 2.2 Specifications of Actigraph GT3X+

Acceleration Sensor Type	MEMS Range +/- 6g
Transducers	Tri-axis, solid state accelerometer. Ambient Light Photodiode
Dimensions	4.6cm x 3.3cm x 1.9cm
Weight	19 g
Water Resistant	Resistant (up to 1 meter for 30 minutes)
Battery Life	31 Days (Fully Charged)
Communication	Full-Speed USB 2.0

2.7.2. Geneactiv

The Geneactiv (Activinsights Ltd., Cambridgeshire, UK) is a tri-axial accelerometer. It also records time varying accelerations with magnitude ranging from ±6g. Technical features of Geneactiv are very similar to those of Actigraph GT3X+. However, the former is more cos effective. In addition, Geneactiv also offers a temperature sensor to help improve the confirmation of wear and non-wear time. Specifications of the device are presented in **table 2.3**.

Table 2.3 Specifications of Geneactiv

Acceleration Sensor Type	MEMS Range +/- 8g
Temperature Sensor Type	Linear active thermister
Dimensions	43mm x 40mm x 13mm
Weight	16g
Water-resistant	upto 10m(IP67 – 1m 24hrs)
Maximum Logging Periods	45 days @ 10Hz, 7 days @ 100Hz
Communication	USB 2.0 Full Speed

2.7.3. Actiheart

Actiheart is a chest mounted, combined unit synchronized heart rate monitor and accelerometer capable of storing time-sequenced data. The main component of the Actiheart is 7 mm thick with a diameter of 33 mm and holds a movement sensor, a rechargeable battery and a memory chip. The main unit is attached to a smaller unit through a wire of approximately 100 mm length. Actiheart can measure acceleration, heart rate, heart rate variability, and ECG amplitude. The available epoch settings are 15 sec, 30 sec, or 1 min. It is light-weight and waterproof. Specifications of the device are presented in **table 2.4**.

Table 2.4 Specifications of Actiheart.

Components	Single-unit that includes a main sensor and left leadconnected by a 100mm. wire
Dimensions	Main sensor — Thickness: 0.7 cm., Diameter: 3.3 cm.Left lead — 0.5 × 1.1 × 2.2 cm.
Weight	10 g
Storage Capacity	128kb (15 days with 60s epochs)
Rechargeable Battery	17 mAh Lithium; 3.0 volt, Life: ~14 days continuous wear,Recharge Time: 11 hrs.
Accelerometer frequency range	1–7 Hz
ECG sampling frequency	128 Hz
Measurable heartrate range	31–250 bpm

All three accelerometers have been validated in European populations and have been categorized as class IIa medical devices conforming to the essential safety and health requirements.

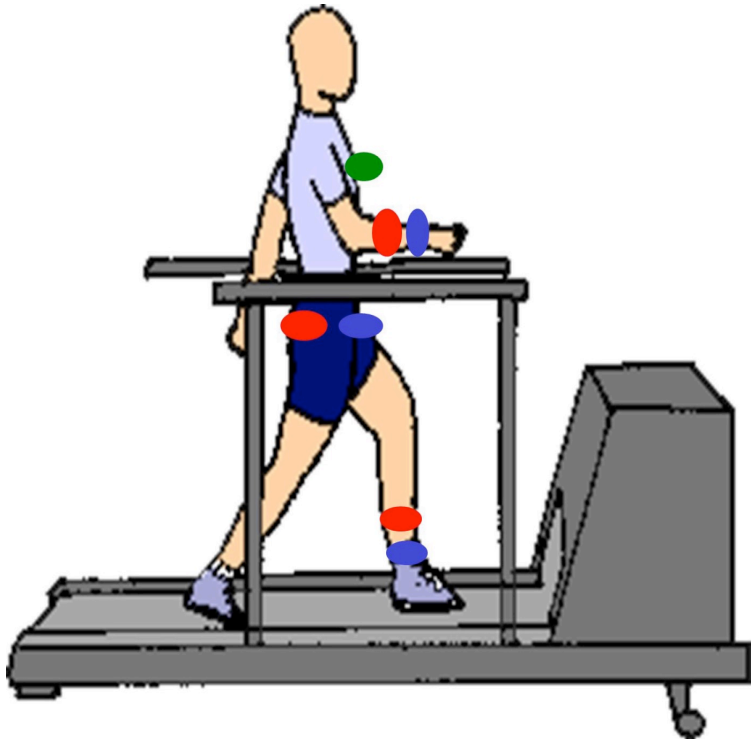
2.7.4. Position of the accelerometers

Before installing the Actiheart, subjects had to undergo skin preparation which includes cleaning the skin to remove any dirt/oil and rubbing with an abrasive material to remove the top layer. For best signals, one electrode is adhered at v1 or v2 (ECG lead positions) and the second electrode is placed approximately 10cm away on the left side at v4 or v5. However, because of the attachment of ECG leads during the ETT, the placement was adjusted to prevent any interference with the ECG leads.

The Actigraph GT3X+ and Geneactiv were mounted on comfortable elasticated bands/belts and each worn on the wrist, ankle and waist.

During the validation experiment (**objective 1**), each participant wore *three Actigraph GT3X+* devices (wrist, ankle and waist), *three Geneactiv* devices (wrist, ankle and waist) and *one Actiheart* (chest, no alternate positions possible), to enable comparison between devices and positions (i.e. *a total of seven devices across four positions,* **figure 2.1**). The accelerometers were worn by the participants while completing the treadmill test. All devices were used according to manufacturer instructions.

Figure 2.1 Positioning of physical activity accelerometers during the ETT. Each participant wore one **Actiheart** (chest only, no alternate position possible), three **Actigraph GT3X+** devices (wrist, ankle and hip) and three **Geneactiv** devices (wrist, ankle and hip); total of seven devices across four positions.



For measuring physical activity in free living conditions, all participants were instructed to wear the accelerometer on the waist over full 7 days and nights continuously, except during water based activities (swimming, bathing or taking a shower) and to follow their normal daily routine. Participants were contacted on alternate days to ensure they were wearing the device. The accelerometers were returned at the end of the 7-day study period.

2.8. Analysis of physical activity data

2.8.1. Objective 1

Physical activity monitoring accelerometers were initialized to capture acceleration at a frequency of 100 Hz in 1-minute epochs. Data from the accelerometers were downloaded to the computer and saved as Microsoft excel files. Freedson Treadmill equation was used to calculate energy expenditure for Actigraph GT3X+ and Geneactiv in terms of Metabolic Equivalents (METs). Actiheart software used the branched chain equation[144] for calculating energy expenditure. The energy expenditure (METs) measured by the devices was calculated as the average of minutes 2 and 3 for each completed 3-minute stage of the treadmill test.

2.8.2. Objective 2 and 3

Accelerometer data were analysed using the manufacturer software (Actilife version 6.10.4). Non-wear time was identified and removed from analysis using the Troiano et al algorithm[230]. The algorithm identified periods of consecutive 60 minutes with zero acceleration recorded allowing a spike tolerance of 2 minutes, indicating that the device had not been worn during that hour. Participants who had worn the accelerometer for less than 7 days and for less than 10 hours per day (averaged over the 7 days) were excluded from final analysis.

Raw acceleration measured by the Actigraph GT3X+ was converted into counts, based on the vector magnitude (i.e. the sum of acceleration in all three axes). Counts are directly proportional to the frequency and intensity of the raw acceleration and hence the physical activity performed. Counts were used to classify data collected from the accelerometer into level of energy expenditure. The cut points defining different physical activity intensities were: (i) Light: 0 - 2690 counts per minute

(CPM), (ii) Moderate: 2691 - 6166 CPM, (iii) Vigorous: 6167 - 9642 CPM, (iv) Very Vigorous: 9643 - ∞ CPM. Time (minutes per week) spent in different physical activity intensity categories was based on the above-mentioned cut points.

The Freedson VM3 Combination (2011) algorithm[231] was used to calculate kilocalories consumed during physical activity over the 7-day period. This option combines the Freedson VM3 (2011) formula with[231] the Williams Work-Energy (1998) equation[232]. Freedson VM3 (2011) equation uses vector magnitude to estimate energy expenditure, which is only valid if the epoch counts exceed 2453 per minute. For counts less than 2453 per minute, Williams Work-Energy (1998) equation is used.

Metabolic Equivalents (METs) per minute were calculated from vertical axis counts using the Freedson adult (1998) equation[233]. METs were then summed over the recording period to calculate MET.minutes in total physical activity over the 7-day period. MET.minutes were also calculated for light (METs<3), moderate (3-6 METS) and vigorous (METS>6) physical activity performed over the 7-day period.

2.9. Statistical analysis

2.9.1. Objective 1

Data were analysed using Statistical Package for the Social Sciences (SPSS) 22.0. I analysed the relationship between Measured and Actual energy expenditure using two complementary approaches. First, I calculated the *difference* between Measured and Actual energy expenditure for each participant at each stage. I then compared the difference between Measured and Actual between devices and positions (using Analysis of Variance), and investigated whether ethnicity or other

clinical covariates were associated with the extent of the difference between Measured and Actual energy expenditure (using linear regression).

Next, I used linear regression to quantify the relationship between Measured and Actual energy expenditure across all stages of the treadmill test for each participant; here the beta co-efficient from linear regression provides an estimate of the change in Measured energy expenditure per unit change in Actual energy expenditure during exercise. I then compared beta-coefficients between device and positions (using analysis of variance), and again explored whether ethnicity or other clinical covariates influenced the relationship between Measured and Actual energy expenditure (using linear regression).

2.9.2. Objectives 2 and 3

Statistical analyses were performed using SPSS version 22. Statistical significance was inferred at a P value of <0.05. Continuous data was expressed as mean ± standard deviation (SD), and categorical data as percentage (%). Distribution of the study variables was assessed using histograms. Univariate tests of the differences were carried out between South Asians and Europeans using the independent samples t-test and chi squared test for continuous and categorical variables respectively. Pearson's correlation co-efficient was used for initial univariate assessment of the relationships between continuous variables. Finally, multivariate linear regression was used to investigate the relationships between ethnicity, physical activity, insulin resistance and related metabolic disturbances, taking account of potential confounding effects.

During sensitivity analysis, logarithmic transformation was used for positively skewed data. For these variables, geometric means are presented along with approximate standard deviations derived using the variance transformation formula. Contribution of physical activity to the increased risk of T2D in South Asians was assessed using multiple linear regression. Adjustment for potential confounders was made during all analyses.

2.9.3. Objective 4

Statistical analysis was performed using SPSS 23. Continuous data was expressed as mean ± standard deviation (SD), and categorical data as percentage (%). Distribution of study variables was assessed using histograms and logarithmic transformation of positively skewed data (glucose, insulin, HOMA-IR and physical activity measures) was carried out to restore the normal distribution. I initially carried out univariate tests of the differences between South Asians and Europeans using the independent samples t-test and chi squared test for continuous and categorical variables respectively. P value < 0.05 was considered significant.

2.9.3.1. Imputation of accelerometer data

I measured physical activity objectively using Actigraph GT3X+ accelerometer amongst 682 LOLIPOP participants (**chapter 4**). I used data from these 682 participants to impute the accelerometer data. The data was divided into discovery and replication sets which allowed validation of the prediction equations. Two-thirds of the sample (*n* = 473) was randomly assigned to a discovery group, from which the prediction equations were derived. The remaining one-third of the sample (*n* = 209) was used for cross validation.

Multiple linear regression modelling was used to develop prediction equations for estimation of physical activity as measured by accelerometer amongst South Asians and Europeans. The imputation function was developed using the Actigraph GT3X+ accelerometer data as the outcome measure. Logarithmic transformation of the outcome variable was carried out to restore the normal distribution. The imputation model included demographic (ethnicity, sex, age, and family history of type 2 diabetes, hypertension and coronary heart disease), anthropometric (weight, height, body mass index, waist-hip ratio and waist and hip circumference) and biochemical measures (fasting glucose, HbA1c, cholesterol, triglycerides, LDL-C and HDL-C) as potential predictors.

Coefficient of determination (R^2) from the discovery and replication sets were used to evaluate the precision of the equations. Equations with a high R^2 were considered the best prediction models. In addition, the prediction equations were considered to cross-validate if the slope and intercept between the actual and predicted accelerometer MET.minutes was 1 and 0 respectively in the discovery set and the paired Student's *t* test, for actual and predicted accelerometer MET.minutes in the replication set, was not significant.

I used the imputed accelerometer data to determine the contribution of physical activity to new onset T2D amongst South Asians.

2.9.3.2. Effect of physical activity on glucose, insulin resistance and new-onset T2D

Linear regression analysis was carried out to determine the association of physical activity (questionnaire and imputed accelerometer MET.minutes) with

glucose, insulin and HOMA IR. Confounding variables like age, sex and ethnicity were controlled by stratification. Meta-analysis was then performed to get an average effect size. The positively skewed outcome variables (glucose, insulin, and HOMA-IR) and the predictors (physical activity measure) were log transformed to restore normal distribution. Beta coefficient from linear regression represents the unit change in the outcome variable with every unit change in PA measure.

Logistic regression was carried out to determine the effect of physical activity on T2D incidence. Age, sex and ethnicity were controlled by stratification and meta-analysis was performed to obtain average effect size. The average effect size represents the relative risk of new-onset T2D for increase in physical activity.

2.10. My contributions to the study

Designing the research

South Asia is home to one of the largest populations of people with T2D and associated complications. Adoption of sedentary lifestyle because of the rapid urbanization and mechanization has led to decreased physical activity, further fuelling the epidemic of T2D amongst South Asians. However, the contribution of PA levels to T2D remained undetermined. Since majority of the population living in South Asians countries belong to the lower or middle socioeconomic group, preventing and controlling T2D by increasing physical activity will provide a cost-effective way to improve the health status in these countries. Therefore, it was important to explore and quantify the contribution of physical activity to the high burden of T2D in South Asians.

To determine the effect of physical activity on T2D, the most important step was to find an accurate and objective way of quantifying physical activity in the South Asian population. After doing extensive research on accelerometers, I discovered that three most widely used accelerometers in both cross sectional and prospective studies are (i) Actigraph GT3X+, (ii) Geneactiv and (iii) Actiheart. Hence, first ste p was to determine which accelerometer was the most accurate to be used in the South Asian population, followed by objective measurement of routine physical activity, and exploring the association between physical activity and T2D in South Asians.

Data collection

Objective 1: To find the most accurate and reliable physical activity measuring accelerometer in South Asians and Europeans, I conducted a study where I compared the energy expenditure calculated by three types of accelerometers to the standard energy expenditure determined using the exercise treadmill test. I contacted the respective companies to get each type of accelerometer on loan for 1 year. I requested for 3 devices from each company to test different body positions simultaneously. After getting ethical approval from the local REC, I collaborated with the physiologists working at the Ealing hospital NHS Trust to recruit participants from their chest pain clinics where patients were referred to undergo an exercise tolerance test according to the Bruce protocol. Participant recruitment was a major challenge for this study. Total duration of the clinics was only 20-minutes. I had to consent the participants, take measurements and position the devices during this limited time. Moreover, participants were supposed to have a blood pressure monitoring cuff on one arm and 12 ECG leads, so attaching 7 more physical activity devices to the participants was challenging. I was present throughout the exercise test and collected all the data myself which included an informed written consent from the participants,

collecting a brief medical and personal history, carrying out physical measurements, preparation of the skin before putting on the devices, positioning all the devices, standing with them throughout the treadmill test to guide them and answer any query that may arise and collecting devices and downloading the data after the treadmill test finished.

Objective 2 and 3: I collected 7-day physical activity data from the participants of LOLIPOP study using the Actigraph GT3X+ accelerometer. I was present while the research clinics were being conducted and provided help when required (collecting blood samples, assessing ECGs and patient follow-up in case of any finding). At the end of each research clinic I conducted a physical activity session which lasted for 20 to 30 minutes. Every participant was seen individually. In these sessions I offered them information (in written and verbal) regarding accelerometers and the importance of measuring physical activity in the population. I explained to them in detail about the procedure they should follow while wearing accelerometers for the next seven days. Being multilingual (English and major South Asian languages-Urdu, Hindi and Punjabi) I could understand and appreciate the participants concerns better and communicated with them more effectively. After taking an informed written consent, I positioned the accelerometers on the participant's waist. I contacted all participants via telephone on alternate days to remind them about wearing the accelerometer and to address any problem they might be having with the accelerometer. Finally, downloaded and saved the raw data using dedicated software after the accelerometers were returned.

Data analysis

I analysed all the data collected for my thesis which involved (i) selecting the correct statistical tests (ii) preparing and analysing the data I collected using the relevant statistics package and (iii) interpreting the findings properly. I learned and conducted various basic and advanced statistical tests on my data. Analysis of raw accelerometer data was most challenging. I attained extensive training to understand the accelerometer data and learned all the steps involved in cleaning the raw accelerometer data and converting it into energy expenditure units (metabolic equivalents). I learned in detail about the software (ActiLife) associated with Actigraph accelerometer data processing.

Chapter 3: Evaluation of three accelerometer devices for measurement of physical activity amongst South Asians compared to Europeans.

3.1. Abstract

Background. Contribution of physical inactivity to the increased risk of T2D amongst South Asians compared to Europeans is not known. Here I evaluated the performance of three commercially available accelerometer devices for objective measurement of physical activity, to assess their potential validity for use in observational population studies of T2D amongst South Asians.

Methods. I investigated 62 South Asian and 40 European men and women aged 25 to 75 years. All participants completed an exercise treadmill test (Bruce protocol) while wearing 3 commercially available accelerometers in manufacturer recommended positions: i. Actigraph GT3X+ ([GT3X+] on ankle, waist and wrist); ii. Geneactiv ([GA] on ankle, waist and wrist) and iii. Actiheart ([AH] on chest only). Personal and medical history was collected by questionnaire, followed by anthropometric measurements. I compared the relationships between energy expenditure measured by the accelerometers (Measured) and actual energy expenditure on the treadmill (Actual) in the two ethnic groups, and tested for potential confounding effects.

Results. All three accelerometery devices under-reported physical activity energy expenditure, in all the positions evaluated. The difference between Measured and Actual energy expenditure was smallest for the GT3X+ in the ankle position (Measured - Actual at peak exercise: $GT3X+_{ankle}$ -6.52 (1.77) Mets; $GT3X+_{waist}$ -8.46 (1.29) Mets; $GT3X+_{wrist}$ -11.17 (1.03) Mets; GA_{ankle} -8.17 (1.19) Mets; GA_{waist} -10.24 (0.64) Mets; GA_{wrist} -11.21 (1.10) Mets; AH_{chest} -9.09 (1.43) Mets, $P<0.001$). The difference between Measured and Actual energy expenditure was similar amongst South Asians and Europeans for the $GT3X+_{ankle}$ ($P>0.05$). The relationship between Measured and

Actual energy expenditure for the GT3X+$_{ankle}$ was also not influenced by age, sex, height, waist, weight or waist-hip ratio (all P>0.05).

Conclusion. Amongst the devices and positions tested, the Actigraph GT3X+ worn on the ankle is the most accurate device for measuring energy expenditure during an exercise treadmill test amongst both South Asians and Europeans. Accelerometer performance is similar in South Asians and Europeans, and does not appear to be influenced by the anthropometric differences between the two populations.

3.2. Aim

To evaluate three accelerometer devices for measurement of physical activity amongst South Asians compared to Europeans.

3.2.1. Objectives

I aimed:

i. To investigate the efficacy of three widely used accelerometers (Actigraph GT3X+, Geneactiv and Actiheart) amongst South Asians and Europeans.

ii. To identify the accelerometer that performs best in both South Asians and Europeans.

iii. To compare the efficacy of accelerometers between South Asians and Europeans.

3.3. Background

Type 2 diabetes (T2D) is a major public health problem worldwide, particularly in rapidly urbanising countries such as India and Pakistan. South Asians (i.e. people originating from India, Pakistan, Bangladesh, or Sri Lanka)[22], who comprise a quarter of the world's population, are at higher risk of T2D than are North Americans and Europeans[8,9]. T2D is estimated to affect more than 100 million people in India alone by 2030[5]. Improved understanding of the mechanisms underlying the high incidence of T2D among South Asians is needed to help reverse the epidemic of T2D in this population[234].

Type 2 diabetes is a complex multifactorial disease determined by both genetic and environmental factors[235]. Genome-wide association studies among South Asians and Europeans have identified common genetic variants at about 80 genetic loci that affect the risk of T2D although these only explain about 5% of T2D risk in both populations[114,115,236]. Unfavorable diet[128,237] and obesity[127] are major risk factors for T2D in South Asians, as they are in other populations, but differences in the prevalence of these risk factors do not seem to account for their increased risk of T2D amongst South Asians.

Physical inactivity is a major risk factor for T2D[101,179,180]. Cross-sectional and prospective studies report a ~30% lower risk of T2D amongst physically active people compared to those with sedentary lifestyles[238]. Furthermore, intervention studies show that increased physical activity reduces the risk of developing T2D by almost 58%[50,171]. Almost 60% of the adult global population fail to reach the WHO minimum physical activity recommendations[239], and physical inactivity may account for ~18% of T2D worldwide[8,100,240-246].

Previous studies report that physical activity is ~50% lower amongst South Asians than Europeans[201,202,247], suggesting that physical inactivity may be an important contributor to increased risk of T2D amongst South Asians. However, all previous studies comparing physical activity levels between South Asians and other populations have relied on physical activity questionnaires, a measurement tool limited by low accuracy, poor reproducibility, linguistic, cultural and reporting bias[248,249]. There is an urgent need for more accurate quantification of physical activity and its contribution to T2D amongst South Asians.

Direct measurement of physical movement using triaxial accelerometers offers the potential for objective quantification of energy expenditure during physical activity in both laboratory[208,218,219] and free-living settings[210,216]. Several devices that measure physical activity using accelerometery have been validated in European populations[228], through comparisons with metabolic measurement of energy expenditure. However, body habitus is known to influence the accuracy of accelerometers[250]. Given the well-documented anthropometric differences between South Asian and European populations[7,13,41], this raises the possibility that accelerometers may provide biased or less accurate results amongst South Asians compared to Europeans. The purpose of the present study was therefore to investigate the performance of 3 commonly used, commercially available accelerometers: the Actigraph GT3X+, Geneactiv and Actiheart amongst South Asians and Europeans.

3.4. Methods

I completed an observational study to assess the accuracy of three commercially available accelerometers for measuring physical activity amongst South

Asians and Europeans. Graded physical activity was induced by a standard exercise treadmill test (Bruce protocol), and the devices positioned on the recommended anatomical locations to assess the importance of positioning on device performance. The study was approved by a Research ethics committee (Ref: 12/WA/0400) and all participants gave written consent to take part.

3.4.1. Participants

I studied 62 South Asian and 40 European men and women, aged 25 to 75 years. Participants were recruited from amongst patients undertaking an exercise treadmill test for clinical indications at Ealing Hospital NHS Trust. Participants were excluded if they stopped before 3 minutes (stage 1) of the treadmill test or had any physical limitation that would affect their performance on the treadmill.

Data was collected regarding personal, behavioural, family and medical history through an interviewer-administered questionnaire. Physical measurements included height, weight, waist circumference and hip circumference. Height was recorded to the nearest 0.1cm using a stadiometer, mounted on a hard, flat surface. Weight was recorded to the nearest 0.1kg. Waist and hip measurements were recorded to the nearest 0.1cm using a non–stretchable measuring tape. Waist circumference was defined as the minimum circumference between iliac crest and lowest rib. Hip circumference was defined as the maximum circumference over the greater trochanters and buttocks.

3.4.2. Accelerometers

I investigated three commercially available accelerometers: i. the Actigraph GT3X+, ii. Geneactiv and iii. Actiheart**.** The Actigraph GT3X+ and Geneactiv are tri-axial accelerometers. Actiheart is a chest worn monitor that records both accelerometery and heart rate to estimate physical activity.

To enable comparison between devices and positions, each participant wore three Actigraph GT3X+ devices (wrist, ankle and waist), three Geneactiv devices (wrist, ankle and waist) and one Actiheart (chest, no alternate positions possible) while completing the treadmill test (i.e. a total of seven devices across four positions). All devices were used according to manufacturer instructions, and using the manufacturer's software for data processing and analysis.

Physical activity monitoring accelerometers were initialized to capture acceleration at a frequency of 100 Hz in 1 minute epochs. Data from the accelerometers were downloaded to the computer and saved as Microsoft excel files. Freedson Treadmill Adult (1998) equation was used to calculate energy expenditure for Actigraph GT3X+ and Geneactiv. Actiheart software uses the branched chain equation[251] for calculating energy expenditure. The energy expenditure measured by the devices was calculated as the average of minutes 2 and 3 for each completed 3-minute stage of the treadmill test.

3.4.3. Exercise treadmill test

Participants completed a graded exercise treadmill test with 12-lead ECG and blood pressure monitoring. The speed and incline of the treadmill increased at 3 minute intervals according to the standard Bruce protocol[252,253]. The test was concluded

according to clinical indication[254]. Actual energy expenditure (METs) was derived by exercise testing software (GE Cardiac Assessment System for Exercise Testing 8000) based on the speed and grade of the stage completed on the Bruce protocol[255]. The equation for Metabolic Equivalents follows: METs = speed x 26.8 x (0.1 + 1.8 x grade/100) + 3.5/3.5, where grade is given in percent and speed is given in miles per hour. MET levels are extrapolated between stages of exercise. Two minutes of a stage must be completed to obtain full stage MET values. At any point thereafter, full credit is given for the stage.

3.5. Statistical analysis

Data were analysed using SPSS 22.0. I analysed the relationship between Measured and Actual energy expenditure using two complementary approaches. First, I calculated the *difference* between measured and observed energy expenditure for each participant at each stage. I then compared the difference between Measured and Actual between devices and positions (using Analysis of Variance), and investigated whether ethnicity or other clinical covariates were associated with the extent of the difference between Measured and Actual energy expenditure (using linear regression). Next, I used linear regression to quantify the *relationship* between Measured and Actual energy expenditure across all stages of the treadmill test for each participant; here the beta co-efficient from linear regression provides an estimate of the change in Measured energy expenditure per unit change in Actual energy expenditure during exercise. I then compared beta-coefficients between device and positions (using analysis of variance), and again explored whether ethnicity of other clinical covariates influenced the relationship between Measured and Actual energy expenditure (using linear regression).

Power

This sample size gave 80% power to detect a correlation of 0.3 between Actual and Measured physical activity at 5% significance for each of the devices. In addition, the sample size enabled me to identify a difference in correlation co-efficient between South Asians and Europeans of 0.4 with 80% power at 5% significance.

3.6. Results

3.6.1. Characteristics of participants

Baseline characteristics of participants are presented in **table 3.1**. South Asians had lower height, but higher waist-hip ratio, compared to Europeans. Weight and body mass index were similar, and time spent on the treadmill was higher in Europeans compared to South Asians.

3.6.2. Comparison of devices

All devices underestimated energy expenditure in the active stages (stages 1-4) of treadmill ($P<0.001$, **table 3.2** and **figure 3.1**). The difference between Measured and Actual energy expenditure increased with each stage of the treadmill test **(figure 3.1**). The difference between Measured and Actual energy expenditure was lower for Actigraph GT3X+ in all the three positions compared to Geneactiv ($P<0.05$, **table 3.2**). The difference between Measured and Actual was also lower for Actigraph GT3X+ in the ankle and waist positions, compared to Actiheart ($P<0.05$, **table 3.2**).

Table 3.1 Clinical characteristics of participants. Results are presented as mean (SD) for continuous variables or as percentage for categorical variables. P values are for the difference between south Asians and Europeans, calculated by regression analysis with adjustment for age and sex.

	Europeans	**South Asians**	**P**
N	40	62	
Age (years)	52.9 (14.0)	51.2 (12.8)	0.5
Male %	52.5%	58.1%	0.7
Type 2 Diabetes (%)	15.0%	8.1%	0.3
Hypertension (%)	25.0%	43.5%	0.06
CHD (%)	15.0%	22.6%	0.5
Smoking (%)	42.5%	25.8%	0.09
Height (cm)	168.0 (10.7)	164.7 (8.9)	0.002
Weight (cm)	76.3 (17.8)	75.3 (12.6)	0.5
Body mass index	27.0 (5.9)	27.7 (3.9)	0.5
Waist circumference (cm)	91.3 (14.3)	94.8 (11.0)	0.2
Hip circumference (cm)	104.2 (11.5)	104.4 (9.3)	0.9
Waist hip ratio	0.9 (0.1)	0.9 (0.1)	0.048
Time on treadmill (minutes)	9.3	8.0	0.01

Table 3.2 Mean difference between Measured (from the accelerometery device) and Actual (from the treadmill test) energy expenditure (METs) during graded exercise test. P-values are for the difference between Measured and Actual (paired samples t-test).

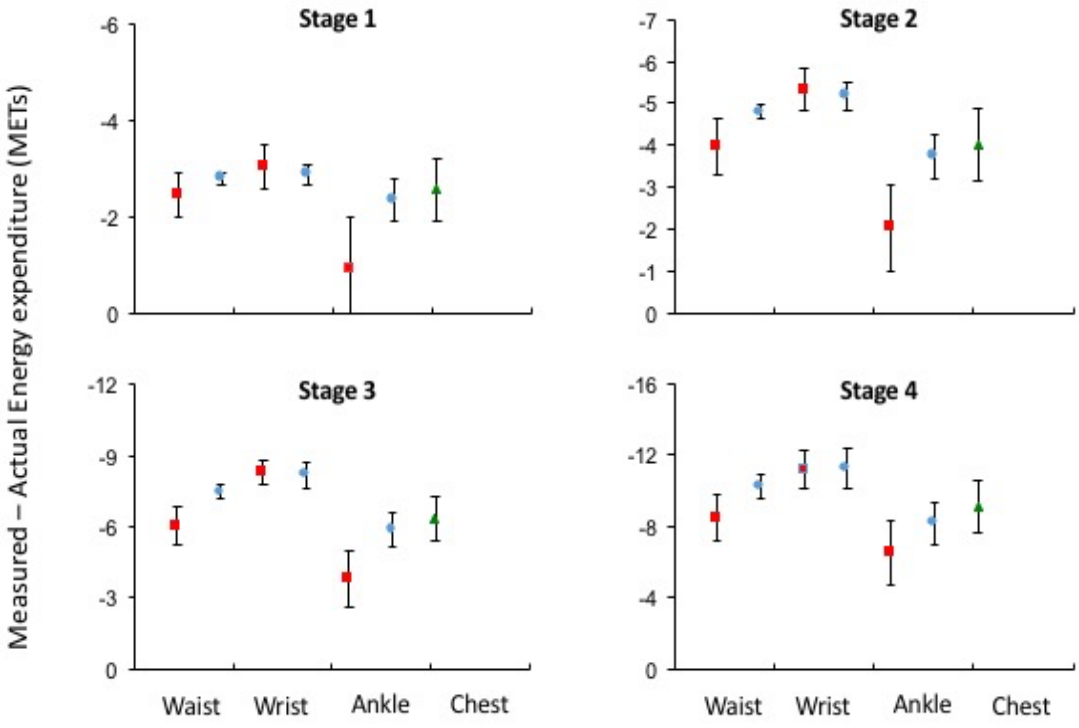
Device	**Rest (1.2)**	**Stage 1 (4.6 Mets)**	**Stage 2 (7.0 Mets)**	**Stage 3 (10.1 Mets)**	**Stage 4 (13.4 Mets)**
Actigraph-GT3X+					
Ankle	-0.07 (0.17)	-0.91 (1.08)	-2.03 (1.03)	-3.81 (1.19)	-6.52 (1.77)
Waist	-0.06 (0.22) [1]	-2.45 (0.44)	-3.95 (0.66)	-6.02 (0.81)	-8.46 (1.29)
Hand	0.06 (0.27) [2]	-3.03 (0.46)	-5.33 (0.49)	-8.29 (0.52)	-11.17 (1.03)
Geneactiv					
Ankle	0.21 (0.15)	-2.34 (0.43)	-3.73 (0.54)	-5.87 (0.75)	-8.17 (1.19)
Waist	0.20 (0.19)	-2.78 (0.14)	-4.80 (0.18)	-7.45 (0.29)	-10.24 (0.64)
Hand	0.11 (0.19)	-2.86 (0.19)	-5.18 (0.34)	-8.19 (0.56)	-11.21 (1.10)
Actiheart					
Chest	-0.05 (0.18) [3]	-2.55 (0.66)	-4.03 (0.86)	-6.35 (0.89)	-9.09 (1.43)

All P- values: P<0.001

[1] P=0.008
[2] P=0.021
[3] P=0.006

Figure 3.1 Mean difference between Measured (from the accelerometery device) and Actual (from the ETT) energy expenditure during rest and active stages of graded exercise test.

(Red square: Actigraph GT3X+; Blue circle: Geneactiv; green triangle: Actiheart).



3.6.3. Comparison of positions

Amongst the four different body positions evaluated, devices worn on the ankle showed least difference between Measured and Actual energy expenditure followed by devices worn on the waist and chest **(table 3.2)**. Wrist-worn devices consistently showed highest difference between Measured and Actual energy expenditure. The differences were most evident at peak exercise (Measured – Actual for Actigraph GT3X+ on ankle: -6.52 (1.77); waist: -8.46 (1.29); wrist -11.17 (1.03); Geneactiv on ankle: -8.17 (1.19); waist -10.24 (0.64); wrist: -11.21 (1.10); Actiheart on chest: -9.09 (1.43), P<0.001).

In regression analysis (**table 3.3**), the relationship between Measured and Actual energy expenditure was closer to unity for the Actigraph GT3X+ than the Geneactiv device, at both the ankle and waist positions [beta (SE) values: ankle = 0.55 (0.11) vs. 0.33(0.04), P<0.001; waist = 0.31 (0.04) vs. 0.14 (0.02), P<0.001]. Actigraph GT3X+ also performed superiorly compared to Actiheart in both the ankle and waist positions (p<0.001). There was little relationship between Measured and Actual energy expenditure for wrist worn Actigraph GT3X+ and Geneactiv devices.

3.6.4. Impact of ethnicity and anthropometric measurements on accelerometer output

There was little evidence for heterogeneity in the relationship between Measured and Actual energy expenditure between the two populations for any of the devices or positions tested (all P>0.05, **table 3.4**). In both the populations the relationship between Measured and Actual was closest to unity for the Actigraph GT3X+ in the ankle position (p<0.001) followed by the waist position (P<0.001) while the wrist-worn devices showed a poor relationship between Measured and Actual.

Table 3.3 Relationship between Measured (from the accelerometery device) and Actual (from the treadmill test) energy expenditure (METs) during graded exercise test. Results are based on linear regression with Measured as the dependent variable and Actual as the independent variable. Beta coefficients represent the change in Measured energy expenditure for a 1 unit change in Actual energy expenditure.

	Beta (SE)	**P value**
N = 91		
Actigraph GT3X+		
Ankle	0.55 (0.10)	<0.001
Waist	0.31 (0.04)	<0.001
Hand	0.06 (0.04)	0.16
Geneactiv		
Ankle	0.33 (0.04)	<0.001
Waist	0.14 (0.02)	<0.001
Hand	0.07 (0.02)	0.006
Actiheart		
Chest	0.30 (0.05)	<0.001

Table 3.4 Relationships between Measured (from the accelerometery device) and Actual (from the treadmill test) energy expenditure (METs) during graded exercise test in Europeans and South Asians. Results are based on linear regression with Measured as the dependent variable and Actual as the independent variable. Beta coefficients represent the change in Measured energy expenditure for a 1 unit change in Actual energy expenditure. P_{het} refers to P-value for the heterogeneity of effect between Europeans and South Asians.

	Europeans (37)		**South Asians (54)**		**P_{het}**
	Beta (SE)	**P**	**Beta (SE)**	**P**	
Actigraph GT3X+					
Ankle	0.53 (0.11)	<0.001	0.57 (0.11)	<0.001	0.8
Waist	0.32 (0.04)	<0.001	0.30 (0.05)	<0.001	0.7
Hand	0.06 (0.04)	0.191	0.06 (0.04)	0.151	0.9
Geneactiv					
Ankle	0.32 (0.04)	<0.001	0.34 (0.04)	<0.001	0.7
Waist	0.14 (0.02)	<0.001	0.15 (0.02)	<0.001	0.7
Hand	0.08 (0.02)	0.002	0.07 (0.03)	0.015	0.8
Actiheart					
Chest	0.31 (0.05)	<0.001	0.29 (0.05)	<0.001	0.7

Next, I evaluated whether the relationship between Measured and Actual energy expenditure is influenced by age, sex, anthropometric or other clinical measures. For the Actigraph GT3X+ and Geneactiv devices, there was little evidence these clinical variables impacted on the relationship between Measured and Actual Energy expenditure during the complete treadmill test (all $P>0.05$ after correction for multiple testing, **tables 3.5**). In contrast, for the Actiheart device, lower body mass index and waist circumference were associated with a greater underestimation of energy expenditure during treadmill testing ($P<0.05$ after correction for multiple testing).

Table 3.5 Impact of age, sex, ethnicity and anthropometric measurements on the relationship between Measured (from the accelerometer) and Actual (from the treadmill test) energy expenditure. Beta coefficients represent the change in the relationship between Measured and Actual energy expenditure, associated with the respective clinical variable. P values are calculated by regression analysis with adjustment for age, sex and ethnicity. Statistical significance inferred at P<0.001 (i.e. P<0.05 after conservative Bonferroni correction for multiple testing).

	Actigraph GT3X+						**Geneactiv**						**Actiheart**	
	Ankle		**Waist**		**Wrist**		**Ankle**		**Waist**		**Wrist**		**Chest**	
	Beta	**P**	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**	**Beta**	**P**
Age (years)	-0.001	0.43	-0.002	0.008	-0.001	0.07	0.000	0.92	0.000	0.26	0.000	0.74	0.000	0.83
Sex (female)	-0.032	0.37	0.003	0.89	-0.019	0.23	0.014	0.47	-0.013	0.18	0.018	0.18	0.012	0.64
Ethnicity (South Asian)	0.027	0.45	-0.028	0.23	-0.006	0.72	0.023	0.23	0.007	0.47	-0.007	0.59	-0.02	0.44
Height (cm)	0.000	0.91	-0.003	0.14	0.000	0.85	-0.000	0.97	-0.001	0.05	-0.001	0.41	-0.001	0.48
Weight (kg)	0.001	0.26	-0.002	0.03	-0.001	0.10	0.000	0.54	0.000	0.29	0.000	0.44	**0.004**	**<0.001**
Body mass index (kg/m^2)	0.004	0.27	-0.004	0.12	-0.003	0.11	-0.001	0.58	0.000	0.78	-0.001	0.68	**0.013**	**<0.001**
Waist circumference (cm)	0.002	0.30	-0.001	0.17	-0.001	0.10	0.000	0.73	0.000	0.57	0.000	0.64	**0.005**	**<0.001**
Waist-hip ratio	0.187	0.49	0.227	0.19	-0.097	0.42	0.095	0.52	0.074	0.34	0.035	0.74	0.585	0.003

3.7. Discussion

I show that the Actigraph GT3X+ worn on the ankle or waist measures energy expenditure during a treadmill test more accurately than both the Geneactiv device in similar positions, and the chest-worn Actiheart device. Although all the three devices evaluated consistently underestimate actual energy expenditure, device performance is similar between South Asians and Europeans. The Actigraph GT3X+ and Geneactiv device are not influenced by differences in anthropometric measures. However, for the Actiheart device, the degree of error is increased amongst people with lower levels of adiposity. My results suggest that the Actigraph GT3X+ worn on the ankle or waist is a suitable device for objective measurement of energy expenditure during physical activity amongst South Asians, and for comparison of energy expenditure between South Asian and European populations.

I evaluated the performance of three commercially available accelerometers, for measurement of energy expenditure. Actiheart includes heart rate monitoring in addition to accelerometery, and incorporates this information into estimation of energy expenditure. The Actigraph GT3X+, Geneactiv and Actiheart devices have been validated against actual energy expenditure determined by doubly-labeled water and calorimetry in Europeans in both laboratory and free-living setting[205,208,210,216]. However, measurement of energy expenditure during physical activity accelerometers is closely influenced by both technical factors such as device positioning[223], as well as biological factors such as height, weight, waist-hip ratio and fat mass[250]. These observations suggest that accuracy of accelerometers may vary between South Asians and Europeans as a result of the anthropometric differences between the two populations.

I show that measured energy expenditure from all three accelerometers is lower than the actual energy expenditure, during all stages of the treadmill test. The Actigraph GT3X+ captured energy expenditure more accurately that the Geneactiv device in all positions evaluated. Ankle and waist worn Actigraph GT3X+ devices also performed superiorly to the Actiheart device. This is consistent with previous studies which support the validity of the Actigraph device under both laboratory[219] as well as free-living conditions[210,216]. In contrast, wrist-worn accelerometers showed poor relationship and captured minimal energy expenditure, likely reflecting the relative lack of contribution of hand movement to physical activity during walking[256].

The relationship between Measured and Actual energy expenditure was similar amongst South Asians and Europeans for all devices and positions. These results support the validity of the accelerometers evaluated for comparisons of physical activity and energy expenditure between populations. However, the results also reveal that under-reporting of physical activity by the Actiheart device was greatest amongst people with lower body mass index and lower levels of central obesity, suggesting that this device may be less suitable for use in studies of energy expenditure from physical activity in the general population.

Although I show for the first time the validity of physical activity accelerometers amongst South Asians, our study has some limitations. I compared measured with actual energy expenditure estimated based on speed and incline of the exercise treadmill, rather than directly measured energy expenditure from double labeled water or calorimetry. However, published studies show that estimates of energy expenditure based on speed and incline correlate closely with direct measurements from doubly-labeled water and

calorimetry[257]. Secondly, I studied people in a hospital setting and limited the assessment of physical activity to energy expenditure during walking. Future work should include assessment of device performance under a wider range of activities in free-living conditions.

In summary, I show that the Actigraph GT3X+ is more accurate than the Geneactiv and Actiheart devices for measurement of physical activity during walking, and that energy expenditure during walking is best measured by devices worn on the ankle and waist. The performance of the Actigraph GT3X+ is similar in South Asians and Europeans and does not appear to be materially influenced by anthropometric parameters. My results support the view that the Actigraph GT3X+ is a suitable device for measurement of energy expenditure during physical activity in trans-ethnic epidemiological studies.

Chapter 4: Contribution of physical activity levels to higher risk of Insulin resistance and associated metabolic disturbances in South Asians compared to Europeans.

4.1. Abstract

Background. Insulin resistance and related metabolic disturbances are major risk factors for the higher T2D risk and associated morbidity and mortality amongst South Asians. The contribution of physical activity to the increased prevalence of insulin resistance and related disturbances amongst South Asians is unknown.

Methods. I recruited 902 South Asian and European men and women, aged 35-85 years from the ongoing LOLIPOP study. Clinical characterisation comprised standardised questionnaire and measurement of height, weight, waist and hip circumference and blood pressure. Fasting bloods were taken for assessment of glucose, insulin, lipids and HbA1c. Physical activity was quantified using a validated accelerometer, Actigraph GT3X+, worn for 7 days. Univariate and multivariate approaches were used to investigate the relationship between ethnicity, physical activity, insulin resistance and related metabolic disturbances.

Results. Total physical activity was ~31% (P=0.01) lower amongst South Asians compared to Europeans (Mean MET.minutes [SD]: 1505.2 [52] vs. 2050.9 [86.6], P<0.001). After adjusting for age and sex, total physical activity had a negative association with HOMA-IR (B [SE]: -0.18 [0.08], P=0.04) and fasting glucose levels (B[SE]: -0.11 [0.04], P=0.02). There was no association between physical activity and other glycemic and lipid parameters. Total physical activity per week did not account for the difference in insulin resistance between South Asians and Europeans. In contrast, after adjusting for total physical activity, the difference in fasting glucose between South Asians and Europeans was reduced and no longer statistically significant.

Conclusion. Lower levels of physical activity may contribute to the increased fasting glucose concentrations in South Asians compared to Europeans. My results suggest that

lifestyle modification through increased physical activity may help to improve glucose metabolism and reduce the burden of excess T2D and related complications amongst South Asians.

4.2. Aim

To examine the contribution of physical activity levels to the higher risk of insulin resistance and related metabolic disturbances that predict T2D, amongst South Asians and Europeans.

4.2.1. Objectives

I aimed to investigate:

i. Differences in objective physical activity levels between South Asians and Europeans

ii. Relationship of objective physical activity levels to insulin resistance and related metabolic disturbances

iii. Contribution of physical activity to the higher prevalence of insulin resistance and related metabolic disturbances amongst South Asians

iv. Develop an imputation function using Actigraph GT3X+ accelerometer data as the outcome measure.

4.3. Background

People of South Asian ancestry (originating from India, Pakistan, Sri lanka and Bangladesh) are at high risk of type 2 diabetes (T2D). According to the IDF report 2015, worldwide there were an estimated 415 million South Asians with T2D in 2015, and this number is expected to increase to 642 million by 2040. Population studies from the non-migrant South Asians show that T2D affects ~15% of urban South Asians, compared to ~5% of their rural counterparts[22]. In the UK, prevalence of T2D amongst South Asians is reported to be up to three times higher than in the native European population (22% vs. 7%)[7].

The increased risk of T2D amongst South Asians is closely associated with the presence of insulin resistance and related metabolic disturbances (raised fasting insulin and glucose, central adiposity, high triglycerides and low HDL cholesterol)[44]. Population studies report a higher prevalence of insulin resistance and related metabolic disturbances amongst South Asians compared to Europeans[7,38]. This higher risk of insulin resistance and metabolic disturbances amongst UK South Asians is not explained by differences in common genetic variants, adiposity or dietary macronutrient intake.

Observational and prospective studies show that increased physical activity is associated with improvement in insulin sensitivity and reduction in insulin resistance and related metabolic disturbances[174-178]. A reduction of ~7% ($P<0.05$) in fasting insulin levels has been reported for a 30-minute increase in moderate-intensity physical activity[180]. In addition, physical activity is reported to be associated with improvements in glucose metabolism, reduction in triglyceride concentration and an increase in high-density lipoprotein (HDL)[196,198], even in the absence of weight loss[181,190].

Cross-sectional studies in the UK report that South Asians have lower levels of physical activity than Europeans[200-202], raising the possibility that low levels of physical activity may contribute to the increased risk of T2D in South Asians. However, published studies have almost all used physical activity questionnaires, an approach known to be of limited accuracy and confounded by reporting bias[226]. Moreover, none of the questionnaires used for measuring physical activity levels have been validated for use amongst South Asians. Inaccurate quantification of physical activity levels amongst South Asians is a significant limitation to understanding the potential contribution of physical activity levels towards the higher risk of insulin resistance, associated metabolic disturbances and T2D in South Asians compared to Europeans.

Accelerometers are electronic sensors for objective measurement of physical activity, validated for use in free-living settings[228]. Compared to direct calorimetry and doubly-labelled water, accelerometers provide substantially greater accuracy for quantification of energy expenditure during physical activity than subjective methods (diaries, self-reports, questionnaires). In this study, I quantified physical activity by using accelerometer amongst South Asian and European men and women, to compare physical activity levels between the two populations, and to determine the contribution of physical activity to the higher prevalence of insulin resistance and related metabolic disturbances in South Asians.

4.4. Methods

4.4.1. Participants

I recruited 902 South Asian and European men and women, aged 35-85 years, to the study. All participants were recruited from the ongoing London Life Sciences Prospective Population (LOLIPOP) study amongst South Asians and Europeans. South Asians were defined as having all 4 grandparents born on the Indian subcontinent (India, Pakistan, Sri lanka and Bangladesh); Europeans were of self-reported white ancestry and born in the UK. People with musculoskeletal disorders which impaired habitual physical activity were excluded from the study. This study was approved by the London-Fulham Research Ethics Committee (ref 07/H0712/150), and all participants gave an informed written consent.

4.4.2. Clinical characterisation

Participants attended a dedicated research clinic between 0900h and 1200h following an overnight fast. An interview-administered questionnaire was used to collect data on medical history, family history, current medications, personal and social history. Weight, height, waist circumference, hip circumference and blood pressure were measured by standardised protocols. Weight was measured to the nearest 0.1kg using digital scales mounted on a hard and flat surface. Height, waist and hip circumference were measured to the nearest 0.1cm. Height was measured using a stadiometer, mounted on a hard and flat surface. Waist circumference was defined as the point midway between the iliac crest and lowest rib. Hip circumference was defined as the maximum circumference over the greater trochanters and buttocks. Blood pressure was measured using an OMRON 705CP blood pressure monitor. Three measurements were taken and an average of these was documented.

Fasting venous blood samples were collected for glucose, insulin, lipid profile, urea, electrolytes and HbA1c. Insulin resistance was assessed using the homeostatic model assessment (HOMA- IR), where HOMA-IR = [Glucose (mmol/L) x Insulin (mU/L)] / 22.5. HOMA-IR is a highly validated measure of insulin resistance which correlates closely with the gold standard euglycaemic-clamp method ($r=0.8$, $P<0.05$)[258] for measurement of insulin resistance.

4.4.3. Assessment of physical activity

Physical activity was measured objectively using Actigraph GT3X+, a tri-axial accelerometer that has been validated for assessment of free-living physical activity in Europeans, through comparison with gold standard doubly-labelled water and calorimetry. All participants were asked to wear the accelerometer for 7 consecutive days, and only remove it during water based activities (swimming or bathing). The accelerometer was worn on the waist, using an elasticated belt. Participants were contacted on alternate days to ensure they were wearing the device. The accelerometers were returned at the end of the 7-day study period.

4.4.4. Analysis of physical activity data

Accelerometer data were analysed using the manufacturer software (Actilife version 6.10.4). Non-wear time was identified, using the Troiano et al algorithm[230], and removed from analysis . The algorithm identified periods of consecutive 60 minutes with zero acceleration recorded allowing a spike tolerance of 2 minutes, indicating that the device had not been worn during that hour. Participants who had worn the accelerometer for less than 7 days and for less than 10 hours per day (averaged over the 7 days) were excluded from final analysis.

Raw acceleration measured by the Actigraph GT3X+ was converted into counts, based on the vector magnitude (i.e. the sum of acceleration in all three axes). Counts are directly proportional to the frequency and intensity of the raw acceleration and hence the physical activity performed. Counts were used to classify data collected from the accelerometer into level of energy expenditure. The cut points defining different physical activity intensities were: (i) Light: 0 - 2690 counts per minute (CPM), (ii) Moderate: 2691 - 6166 CPM, (iii) Vigorous: 6167 - 9642 CPM, (iv) Very Vigorous: 9643 - ∞ CPM. Time (minutes per week) spent in different physical activity intensity categories were based on the above-mentioned cut points.

The Freedson VM3 Combination (2011) algorithm was used to calculate kilocalories consumed during physical activity over the 7-day period. This option combines the Freedson VM3 (2011) formula[231] with the Williams Work-Energy (1998) equation[232]. Freedson VM3 (2011) equation uses vector magnitude to estimate energy expenditure, which is only valid if the epoch counts exceed 2453 per minute. For counts less than 2453 per minute, Williams Work-Energy (1998) equation is used.

Metabolic Equivalents (METs) per minute were calculated from vertical axis counts using the Freedson adult (1998) equation[233]. Mets were then summed over the recording period to calculate MET.minutes in total physical activity over the 7-day period. MET.minutes were also calculated for light (METs<3), moderate (3-6 METS) and vigorous (METS>6) physical activity performed over the 7-day period.

4.5. Statistical analysis

Statistical analyses were performed using SPSS version 22. Continuous data was expressed as mean ± standard deviation (SD), and categorical data as percentage (%). Distribution of the study variables was assessed using histograms. Univariate tests of the differences were carried out between South Asians and Europeans using the independent samples t-test and chi squared test for continuous and categorical variables respectively. Pearson's correlation co-efficient was used for initial univariate assessment of the relationships between continuous variables. Finally, multivariate linear regression was used to investigate the relationships between ethnicity, physical activity, insulin resistance and related metabolic disturbances, taking account of potential confounding effects.

Power

Current sample size for each ethnic group enabled me to detect a correlation coefficient difference of 0.2 and a difference of 0.2 SD in physical activity levels amongst South Asians and Europeans with 80% power and 5% significance. In addition, the sample size allowed me to determine a 0.3 SD difference in the levels of metabolic measures among the physically active and physically inactive groups at 5% significance level. This sample size also allowed me to detect 0.2 SD difference in physical activity levels metabolic measures amongst South Asians and Europeans with 80% power and 5% significance.

4.6. Imputation of accelerometer data

I used physical activity data measured objectively using Actigraph GT3X+ accelerometer amongst 682 LOLIPOP participants to impute the accelerometer data. The

data was divided into discovery and replication sets which allowed validation of the prediction equations. Two-thirds of the sample (n = 473) was randomly assigned to a discovery group, from which the prediction equations were derived. The remaining one-third of the sample (n = 209) was used for cross validation.

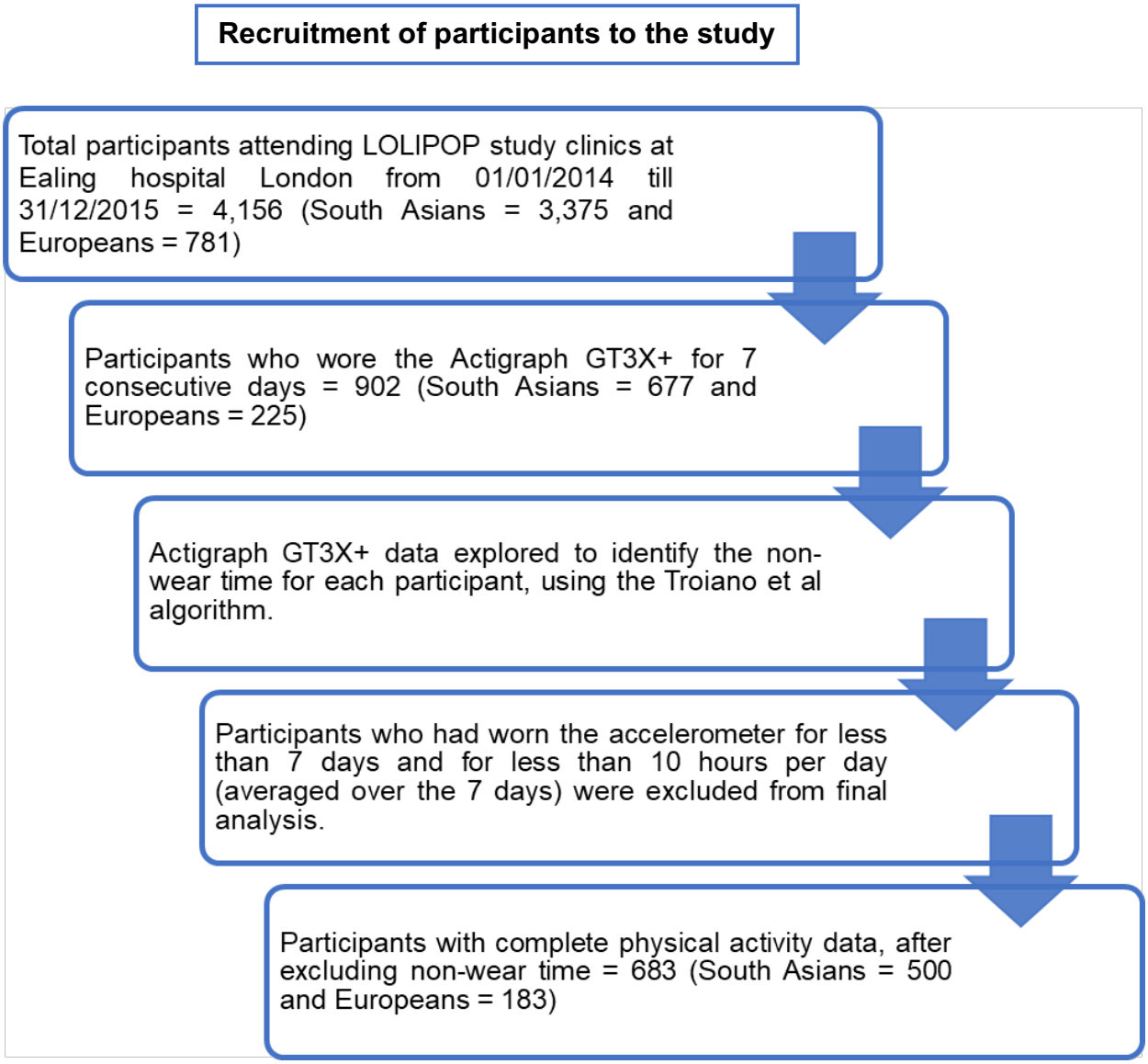
Multiple linear regression was used to develop prediction equations for estimation of physical activity as measured by accelerometer amongst South Asians and Europeans. An imputation function was developed using the Actigraph GT3X+ accelerometer data as the outcome measure. Logarithmic transformation of the outcome variable was carried out to restore normality. The imputation model included demographic (ethnicity, sex, age, and family history of T2D, hypertension and coronary heart disease), anthropometric (weight, height, body mass index, waist-hip ratio and waist and hip circumference) and biochemical measures (fasting glucose, HbA1c, cholesterol, triglycerides, LDL-C and HDL-C) as potential predictors.

The coefficient of determination (R^2) from the discovery and replication sets was used to evaluate the precision of the equation. Equations with a high R^2 were considered the best prediction models. In addition, the prediction equations were considered to cross-validate if the slope and intercept between the actual and predicted accelerometer MET.minutes was closer to 1 and 0 respectively and the paired Student's t test, for actual and predicted accelerometer MET.minutes was not significant in the replication set. I used the imputed accelerometer data to determine the contribution of objective physical activity to new onset T2D amongst South Asians.

4.7. Results

4.7.1. Characteristics of participants

I studied 902 South Asian and European men and women. Out of these, 219 participants did not wear accelerometer for at least 10 hours per day for 7 days and were excluded from analysis. This left 683 participants with complete data (183 Europeans and 500 South Asians), who were used for all analyses.



Clinical characteristics of the participants are shown in **table 4.1**. South Asians were on average younger than Europeans (Mean [SD]: 53 [9] vs. 59 [10], P<0.001). Body mass index was similar (P=0.3), but waist hip ratio higher in South Asians compared to Europeans (Mean [SD]: 0.95 [0.08] vs. 0.92 [0.08], P<0.001). South Asians had higher HOMA-IR, fasting glucose, HbA1c, and fasting insulin compared to Europeans (Percentage difference: 44%, 11%, 9%, and 33% respectively, all P<0.001). Triglyceride levels were higher while HDL cholesterol was lower in South Asians than in Europeans (P<0.001). The prevalence of T2D was ~3 times higher in South Asians compared to Europeans (17.7% vs. 5.9%, P<0.001). Cigarette smoking and alcohol intake was lower amongst South Asians compared to Europeans (P<0.001).

I also compared the clinical characteristics of participants attending the LOLIPOP clinics who wore accelerometers with those who did not wear them. Results are presented in **table 4.2**. Clinical characteristics of Europeans who wore the accelerometer and those who did not, were similar. On the other hand, South Asians who wore the accelerometers were younger and showed a better metabolic health profile than those who did not wear the accelerometer.

Table 4.1 Clinical characteristics of South Asian and European participants. Results are presented as mean (SD) and percentages (%) for continuous and categorical variables respectively. P-values are determined from the independent student t-test (continuous variables) and Fisher's exact test (categorical variables).

	Europeans	**South Asians**	
	Mean (SD)	**Mean (SD)**	**P**
N	183	500	
Age (years)	59.3 (10.1)	56.4 (9.0)	<0.001
Male (%)	42.7	53.1	0.02
Ever smoked (%)	35.3	11.5	<0.001
Type 2 Diabetes (%)	5.9	17.7	<0.001
Hypertension (%)	25.9	35.7	0.01
Coronary heart disease (%)	6.5	8.3	0.4
Height (cm)	167.9 (8.8)	164.0 (9.4)	<0.001
Weight (kg)	78.7 (15.3)	74.1 (14.5)	<0.001
Body mass index (kg/m^2)	27.8 (4.9)	27.4 (4.6)	0.3
Waist circumference (cm)	96.3 (12.6)	96.9 (11.7)	0.5
Hip circumference (cm)	104.3 (9.2)	101.9 (8.4)	0.001
Waist-hip ratio	0.92 (0.08)	0.95 (0.08)	<0.001
Systolic blood pressure (mmHg)	131.3 (17.6)	132.6 (17.4)	0.4
Diastolic blood pressure (mmHg)	78.0 (9.9)	79.2 (10.1)	0.2
Cholesterol (mmol/l)	5.20 (0.97)	4.95 (1.01)	0.002
Triglycerides (mmol/l)	1.18 (0.55)	1.46 (0.86)	<0.001
HDL cholesterol (mmol/l)	1.69 (0.45)	1.44 (0.42)	<0.001
LDL cholesterol (mmol/l)	2.98 (0.91)	2.85 (0.90)	0.07
Glucose (mmol/l)	5.28 (1.08)	5.87 (1.87)	<0.001
HbA1c (%)	5.70 (0.66)	6.21 (1.16)	<0.001
Insulin (mmol/l)	9.79 (6.16)	13.59 (9.39)	<0.001
HOMA-IR (mmol/l)	2.38 (1.71)	3.71 (3.10)	<0.001

Table 4.2 Comparison of clinical characteristics of participants attending the LOLIPOP clinic who wore accelerometers with those who did not wear the accelerometers.

	Europeans			South Asians		
	Accelerometer worn			Accelerometer worn		
	No	Yes	p	No	Yes	p
N	556	225		2698	677	
Age (years)	60.1 (11.1)	58.1 (10)	0.02	60.4 (11.2)	55.8 (9.2)	<0.001
Systolic BP (mm Hg)	133.3 (18.9)	130.8 (17.5)	0.1	135.7 (19.1)	132.3 (17.3)	<0.001
Diastolic BP (mm Hg)	78.3 (10.5)	77.6 (9.7)	0.3	77.6 (10.5)	78.8 (10.3)	0.009
Height (cm)	167.4 (9.6)	168.4 (9.3)	0.2	162.3 (9.8)	164.0 (9.6)	<0.001
Weight (kg)	79.3 (18.1)	78.5 (15.4)	0.5	74.6 (15.1)	74.4 (14.3)	0.7
Body mass index (kg/m2)	28.2 (5.7)	27.5 (4.8)	0.1	28.2 (4.9)	27.5 (4.5)	0.001
Waist circumference (cm)	97.5 (15.2)	95.8 (12.6)	0.1	99.1 (12)	97.2 (11.7)	<0.001
Hip circumference (cm)	104.5 (10.1)	104.1 (9.1)	0.6	102.9 (9.1)	102.3 (8.3)	0.2
Waist hip ratio	0.9 (0.1)	0.9 (0.1)	0.1	1.0 (0.1)	0.9 (0.1)	<0.001
Creatinine (umol/l)	78 (20.7)	76.9 (22.3)	0.5	79.1 (38)	75.2 (19.7)	<0.001
Urea (mmol/l)	5.3 (1.8)	5.2 (1.6)	0.3	4.9 (1.9)	4.7 (1.5)	0.001
Cholesterol (mmol/l)	5.2 (1.1)	5.2 (1)	0.7	4.8 (1.1)	5.0 (1.0)	<0.001
Triglycerides (mmol/l)	1.3 (0.8)	1.2 (0.6)	0.1	1.4 (0.8)	1.4 (0.8)	0.9
HDL-C	1.6 (0.5)	1.7 (0.5)	0.1	1.4 (0.4)	1.5 (0.4)	0.03
LDL-C	3.0 (0.9)	3.0 (0.9)	0.5	2.7 (0.9)	2.9 (0.9)	<0.001
Glucose (mmol/l)	5.4 (1.3)	5.3 (1.2)	0.1	6.0 (1.9)	5.8 (1.7)	0.03
HbA1c (%)	5.8 (0.8)	5.7 (0.7)	0.2	6.4 (1.2)	6.2 (1.1)	0.002

4.7.2. Metabolic health of people achieving recommended activity targets

The clinical characteristics of participants who achieved the minimum recommended volume of physical activity per week (moderate to vigorous physical activity of 600 MET.minutes or more per week) are shown in **table 4.3**. Overall 66% participants performed the recommended 600 MET.minutes or more physical activity per week. Proportion of South Asians engaging in minimum recommended physical activity levels was significantly lower than that of Europeans (50.6% vs. 69.4% respectively, P<0.001). Levels of fasting glucose and HbA1c were lower amongst people who did achieve these international guidelines for physical activity (Mean [SD]: 5.6 [1.4] and 5.9 [0.9] respectively), compared with those who did not (Mean [SD]: 6.0 [2.2] and 6.3 [1.3]; P=0.01 and <0.001 respectively). Hypertension, coronary heart disease and T2D were also less common amongst people who performed the minimum recommended physical activity levels compared to those who did not achieve these international guidelines for physical activity (all P<0.05).

Table 4.3 Comparison of the Clinical characteristics of participants achieving WHO guidelines of 600 MET.minutes/week with those not achieving the guidelines. (P values from independent samples t-test).

	<600 MET.minutes	**>600 MET.minutes**	
	Mean (SD)	**Mean (SD)**	**P**
N	234	449	
Age (years)	60.9 (10.5)	55.3 (8.4)	<0.001
Coronary heart disease (%)	10.1	3.1	0.04
Hypertension (%)	43.1	28.1	<0.001
Type 2 diabetes (%)	18.8	12.5	0.03
Height (cm)	160.4 (8.5)	167.4 (8.9)	<0.001
Weight (cm)	70.8 (15.7)	77.6 (13.7)	<0.001
Body mass index (kg/m^2)	27.4 (5.5)	27.6 (4.2)	0.6
Waist circumference (cm)	96.5 (13.4)	96.9 (10.9)	0.7
Hip circumference (cm)	101.7 (9.9)	103.2 (8.0)	0.04
Waist hip ratio	0.94 (0.09)	0.93 (0.08)	0.1
Systolic blood pressure (mmHg)	133.1 (17.9)	131.8 (16.9)	0.3
Diastolic blood pressure (mmHg)	77.3 (9.9)	79.5 (10.0)	0.005
Cholesterol (mmol/l)	4.95 (1.00)	5.07 (1.00)	0.1
Triglycerides (mmol/l)	1.37 (0.72)	1.39 (0.85)	0.8
HDL-C (mmol/l)	1.53 (0.43)	1.50 (0.45)	0.3
LDL-C (mmol/l)	2.79 (0.93)	2.95 (0.88)	0.03
Glucose (mmol/l)	6.0 (2.2)	5.6 (1.4)	0.01
HbA1c (%)	6.3 (1.3)	5.9 (0.9)	<0.001
Insulin (mmol/l)	12.7 (9.6)	12.3 (7.1)	0.5
HOMA-IR (mmol/l)	3.4 (2.9)	3.2 (2.8)	0.5

4.7.3. Physical activity levels in South Asians and Europeans

Physical activity levels amongst South Asians and Europeans are summarised in **table 4.4** and **figure 4.1.** Total physical activity levels expressed as MET.minutes per week were ~31% lower amongst South Asians than in Europeans (Mean MET.minutes [SD]: 1505.2 [52] vs. 2050.9 [86.6], P<0.001). In addition, compared to Europeans, South Asians showed lower levels of physical activity in all pre-specified intensity domains (light, moderate, vigorous and moderate to vigorous physical activity). Differences in age and sex did not contribute to the observed differences in physical activity between the two populations.

4.7.4. Relationship of physical activity with insulin resistance

The univariate relationships between physical activity and insulin resistance, measured by HOMA-IR, showed a negative correlation between total physical activity levels per week and HOMA-IR (r = -0.1, P = 0.02, **table 4.5**). I used multiple regression analysis to evaluate the relationship between MET.minutes in total physical activity per week and HOMA-IR, after adjusting for differences in age, sex and ethnicity. Results revealed a negative association between total physical activity and HOMA-IR (B [SE]: -0.18 [0.08], P=0.04, **table 4.6**). The relationship between total physical activity and insulin resistance was not changed after adjusting for adiposity. In addition, HOMA-IR amongst people achieving recommended physical activity targets per week was similar to those who failed to achieve the minimum recommended levels of physical activity per week (**table 4.3**).

Table 4.4 Physical activity amongst South Asians and Europeans measured using the Actigraph GT3X+ accelerometer. Results are presented as mean (SD) Met.minutes per week of physical activity in pre-specified intensity domains. P-values are for the difference in physical activity between South Asians and Europeans in regression analysis with adjustment for age and sex.

	Europeans **Mean (SD)**	**South Asians** **Mean (SD)**	**P**
MET.minutes per week			
Light physical activity	769.8 (30.8)	685 (18.5)	0.02
Moderate physical activity	1079.9 (59.8)	731.9 (35.9)	<0.001
Vigorous physical activity	201.2 (19.4)	88.2 (11.7)	<0.001
Moderate to vigorous physical activity	1281.1(68.1)	820.1 (40.9)	<0.001
Total physical activity	2050.9 (86.6)	1505.2 (52)	<0.001

Figure 4.1 Physical activity levels (MET.minutes per week) amongst South Asians and Europeans. Error bars represent standard error of the mean.

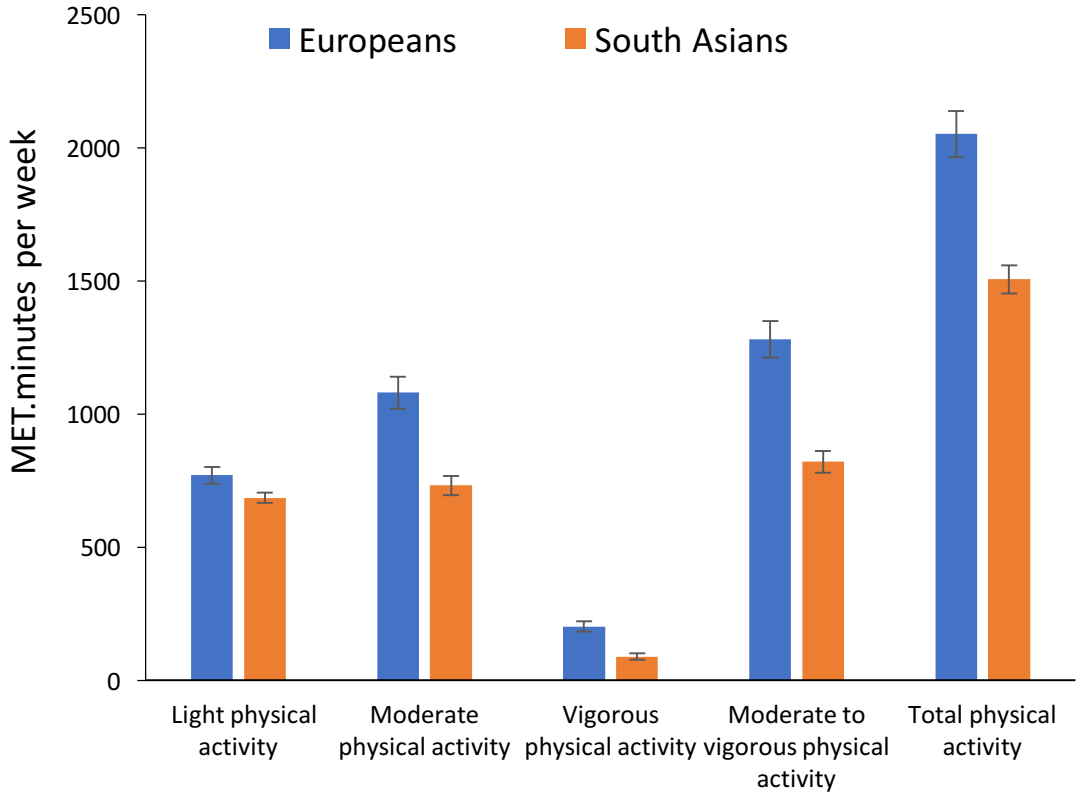


Table 4.5 Correlation (Pearson's correlation) of light, moderate, vigorous, moderate to vigorous and total physical activity energy expenditure (MET.minutes) with insulin resistance and related metabolic disturbances.

	Glucose		HbA1c		Triglycerides		HDL		Insulin		HOMA-IR	
Physical activity measures	**r**	**P**	**r**	**P**	**r**	**P**	**r**	**P**	**r**	**P**	**r**	**P**
MET.minutes per week												
Light physical activity	-0.06	0.13	-0.08	0.03	-0.07	0.05	0.1	0.01	-0.1	0.01	-0.1	0.01
Moderate physical activity	-0.09	0.02	-0.1	0.009	-0.04	0.3	-0.01	0.8	-0.04	0.4	-0.06	0.1
Vigorous physical activity	-0.1	0.007	-0.13	0.001	-0.06	0.1	0.04	0.3	-0.02	0.5	-0.05	0.2
Moderate to vigorous physical activity	-0.11	0.005	-0.12	0.002	-0.06	0.2	0.01	0.9	-0.04	0.3	-0.07	0.1
Total physical activity	-0.11	0.006	-0.13	0.001	-0.07	0.07	0.04	0.3	-0.06	0.1	-0.09	0.02

Table 4.6 Relationship of physical activity with glucose, HbA1c, Insulin and HOMA-IR in regression analysis with adjustment for age, sex and ethnic group. Results are presented as the change (effect [SE]) in glucose or HbA1c per 1000 MET.minutes of physical activity per week.

	Glucose (mmol/l)		**HbA1c (%)**		**Insulin (IU/l)**		**HOMA-IR (mmol/l)**	
	Effect (SE)	**P**	**Effect (SE)**	**P**	**Effect (SE)**	**P**	**Effect (SE)**	**P**
MET.minutes per week								
Light physical activity	-0.11 (0.12)	0.4	-0.09 (0.07)	0.3	-2.0 (1.0)	0.02	-0.58 (0.25)	0.02
Moderate physical activity	-0.16 (0.06)	0.01	-0.06 (0.04)	0.1	-0.30 (0.41)	0.5	-0.18 (0.12)	0.2
Vigorous physical activity	-0.31 (0.19)	0.1	-0.14 (0.12)	0.3	-0.46 (1.02)	0.7	-0.29 (0.39)	0.5
Moderate to vigorous physical activity	-0.15 (0.06)	0.01	-0.06 (0.03)	0.1	-0.28 (0.36)	0.4	-0.16 (0.11)	0.1
Total physical activity	-0.11 (0.04)	0.02	-0.05 (0.03)	0.1	-0.42 (0.28)	0.1	-0.18 (0.08)	0.04

Light physical activity: <3 METs, moderate physical activity: 3-6 METS, vigorous physical activity: >6 METS and total physical activity.

I also evaluated the age, sex and ethnicity adjusted relationship between intensity stratified physical activity categories (Light, moderate, vigorous, and moderate-vigorous physical activity) and HOMA-IR **(table 4.6)**. There was no significant association between moderate, vigorous or moderate to vigorous physical activity and HOMA-IR (all $P > 0.05$). HOMA-IR showed a weak inverse relationship with light physical activity after adjusting for age, sex and ethnicity (B [SE]: -0.58 [0.25], P=0.02), however, this relationship was no longer significant after adjusting for adiposity.

4.7.5. Relationship of physical activity with glycemic and lipid parameters

I investigated the relationship of MET.minutes in physical activity with biochemical measures of glucose and lipid metabolism. MET.minutes per week in total physical activity were inversely correlated with fasting glucose levels ($r=-0.1$, $P<0.05$) and HbA1c ($r=-0.1$, $P<0.05$) (**table 4.5.)**. After adjusting for differences in age, sex and ethnicity, increased total physical activity per week was associated with lower fasting glucose levels. The association between fasting glucose levels and physical activity per week remained significant after additional adjustment for adiposity (**table 4.7**). There were no significant correlations between MET.minutes per week in total physical activity, fasting insulin levels and lipid parameters (**table 4.5**). Multiple regression analysis also showed no evidence for a relationship between total physical activity and HbA1c, fasting insulin levels, HDL cholesterol or triglycerides (**table 4.6**).

An increase in moderate and moderate to vigorous physical activity per week were associated with lower fasting glucose. There was no association between light or vigorous physical activity and fasting glucose levels. The association between fasting glucose levels and categorical physical activity measures remained significant after additional adjustment for adiposity (**table 4.7**). Fasting insulin levels showed a weak

inverse relationship with light physical activity only after adjusting for age, sex and ethnicity, however, this relationship was no longer significant after adjusting for adiposity. There was no evidence for a relationship between light, moderate or vigorous physical activity and HbA1c, HDL cholesterol and triglycerides (**table 4.6**).

4.7.6. Sensitivity analysis

I carried out sensitivity analyses to evaluate the robustness of my findings. Analysis of physical activity levels amongst South Asians and Europeans showed similar results using alternate metrics of physical activity as a sensitivity analysis (total counts, kilocalories and time spent in light, moderate, vigorous, moderate to vigorous, and total physical activity, **table 4.8**). The relationships of physical activity with HOMA-IR, glycemic parameters and lipid parameters were not materially altered using alternate classification schemes for physical activity, log-transformation of positively skewed variables or by inclusion of people with T2D. The weak association of light physical activity with Insulin and HOMA-IR, determined in the primary analysis, was not significant. (**table 4.9, 4.10 and 4.11**).

Table 4.7 Effect of adiposity (body mass index and waist hip ratio) on the relationship between physical activity MET.minutes and fasting glucose levels. Results are presented as the change (effect [SE]) in glucose levels for a 1000 MET.minutes per week increase in physical activity.

	Glucose (mmol/l)	
	Effect (SE)	**P**
MET.minutes per week		
Light physical activity	-0.09 (0.12)	0.5
Moderate physical activity	-0.17 (0.06)	0.009
Vigorous physical activity	-0.37 (0.12)	0.06
Moderate to vigorous physical activity	-0.16 (0.05)	0.005
Total physical activity	-0.11 (0.04)	0.01

Table 4.8 Physical activity levels amongst South Asians and Europeans. Similar results were obtained using alternate metrics of physical activity as a sensitivity analysis (total counts, kilocalories and time spent in light, moderate, vigorous, moderate to vigorous, and total physical activity).

	Europeans **Mean (SD)**	**South Asians** **Mean (SD)**	**P**
Total counts per week			
Vector magnitude counts	4157254.9 (125344.9)	3793311.0 (75306.4)	0.01
Vertical axis counts	2280907.8 (72952.9)	1946203.9 (43829.7)	<0.001
Time in Physical activity (minutes per week)			
Light physical activity	7255.6 (76.3)	7614.5 (45.8)	<0.001
Moderate physical activity	344.5 (16.7)	258.2 (10.1)	<0.001
Vigorous physical activity	22.9 (5.2)	17.1 (3.1)	0.3
Moderate to vigorous physical activity	369.5 (20.2)	277.1 (12.1)	<0.001
Total physical activity	7625.2 (78.9)	7891.6 (47.4)	0.004
Kilocalories per week	4156.6 (152.9)	3248.9 (91.8)	<0.001
Steps Counts	50885.6 (1949.0)	46583.8 (1170.9)	0.06

Table 4.9 Relationship of alternate measures of physical activity with glucose, HbA1c, insulin and HOMA-IR in regression analysis with adjustment for age, sex and ethnic group.

	Glucose (mmol/l)		HbA1c (%)		Insulin (IU/l)		HOMA-IR (mmol/l)	
	Effect (SE)	**P**	**Effect (SE)**	**P**	**Effect (SE)**	**P**	**Effect (SE)**	**P**
Total counts per week								
Vector Magnitude Counts*	-0.01 (0.003)	0.002	-0.01 (0.002)	0.02	-0.07 (0.01)	0.001	-0.02 (0.001)	<0.001
Vertical axis counts*	-0.02 (0.005)	0.003	-0.01(0.003)	0.03	-0.10 (0.04)	0.003	-0.03 (0.01)	0.001
Minutes in physical activity per week**								
Light physical activity	-0.11 (0.05)	0.03	-0.04 (0.03)	0.2	0.03 (0.03)	0.4	-0.003 (0.01)	0.8
Moderate physical activity	-0.59 (0.23)	0.01	-0.21 (0.14)	0.1	-0.4 (0.2)	0.03	-0.1 (0.05)	0.01
Vigorous physical activity	-0.99 (0.72)	0.2	-0.4 (0.4)	0.5	-0.3 (0.5)	0.5	-0.1 (0.1)	0.4
Moderate to vigorous physical activity	-0.48 (0.19)	0.01	-0.17 (0.11)	0.1	-0.3 (0.1)	0.05	-0.1 (0.04)	0.02
Total physical activity	-0.14 (0.05)	0.01	-0.04 (0.03)	0.1	-0.09 (0.03)	0.8	-0.01 (0.01)	0.4
Energy Expenditure per week								
Kilocalories per week***	-0.05 (0.03)	0.05	-0.02 (0.02)	0.3	-0.02 (0.02)	0.3	0.01 (0.05)	0.8

Results are presented as the change (effect [SE]) in glucose or HbA1c for physical activity levels per week:
**per 100000 counts/week*
***per 100minutes/week*
****per 1000 kilocalories/week*

Table 4.10 Relationship of physical activity with glucose in regression analysis with adjustment for age, sex and ethnic group. Variables with a positively skewed distribution have been log-transformed.

	% decrease in Glucose levels (95% CI)	P
Total counts per week		
Vector Magnitude Counts	0.13 (0.05-0.21)	0.001
Vertical axis counts	0.20 (0.07-0.32)	0.002
Minutes in physical activity per week		
Light physical activity	0.10 (0.03-0.22)	0.1
Moderate physical activity	0.78 (0.21-1.34)	0.007
Vigorous physical activity	1.50 (0.29-3.26)	0.1
Moderate to vigorous physical activity	0.65 (0.18-1.11)	0.007
Total physical activity	0.13 (0.01-0.25)	0.03
Energy Expenditure per week		
Kilocalories per week	0.54 (0.08-1.16)	0.09
MET.minutes per week		
Light physical activity	1.99 (1.09-4.98)	0.2
Moderate physical activity	1.98 (0.41-3.52)	0.01
Vigorous physical activity	3.78 (1.07-8.39)	0.1
Moderate to vigorous physical activity	1.84 (0.46-3.19)	0.009
Total physical activity	1.39 (0.30-2.47)	0.01

Results are presented as the percentage decrease in glucose levels for physical activity levels per week:
**per 100000 counts/week*
***per 100minutes/week*
****per 1000 kilocalories or Met.minutes/week*

Table 4.11 Relationship of physical activity with glucose and HbA1c in regression analysis with adjustment for age, sex and ethnic group. T2D cases have also been included in the analysis. Results are presented as the change (effect[SE]) in glucose or HbA1c for physical activity per week: *per 100000 counts/week, **per 100 minutes/week, ***per 1000 kilocalories or MET.minutes/week.

	Glucose (mmol/l)		HbA1c (%)		Insulin (IU/l)		HOMA-IR (mmol/l)	
	Effect (SE)	**P**	**Effect (SE)**	**P**	**Effect (SE)**	**P**	**Effect (SE)**	**P**
Total counts per week								
Vector Magnitude Counts*	-0.01 (0.004)	0.005	-0.01 (0.002)	0.02	-0.06 (0.01)	<0.001	-0.03 (0.001)	<0.001
Vertical axis counts*	-0.02 (0.007)	0.02	-0.01 (0.003)	0.03	-0.09 (0.03)	0.004	-0.04 (0.01)	0.001
Minutes in physical activity per week**								
Light physical activity	-0.13 (0.06)	0.05	-0.05 (0.03)	0.2	-0.03 (0.03)	0.3	-0.004 (0.01)	0.7
Moderate physical activity	-0.49 (0.29)	0.02	-0.2 (0.14)	0.1	-0.3 (0.01)	0.04	-0.1 (0.04)	0.02
Vigorous physical activity	-1.39 (0.91)	0.1	-0.68 (0.4)	0.5	-0.4 (0.5)	0.4	-0.2 (0.2)	0.3
Moderate to vigorous physical activity	-0.44 (0.24)	0.02	-0.18 (0.11)	0.1	-0.2 (0.1)	0.05	-0.1 (0.04)	0.03
Total physical activity	-0.15 (0.06)	0.02	-0.06 (0.03)	0.1	-0.03 (0.01)	0.7	-0.01 (0.01)	0.4
Energy Expenditure per week***								
Kilocalories per week	-0.05 (0.03)	0.09	-0.03 (0.02)	0.3	-0.2 (0.2)	0.3	0.01 (0.01)	0.8
MET.minutes per week								
Light physical activity	-0.1 (0.16)	0.5	-0.1 (0.07)	0.3	-2.0	0.02	-1.0	0.03
Moderate physical activity	-0.15 (0.08)	0.03	-0.06 (0.04)	0.1	-0.3	0.5	-0.2	0.2
Vigorous physical activity	-0.51 (0.24)	0.04	-0.26 (0.12)	0.3	-1.0	0.6	-0.5	0.3
Moderate to vigorous physical activity	-0.16 (0.07)	0.03	-0.06 (0.03)	0.09	-0.3	0.4	-0.2	0.2
Total physical activity	-0.11 (0.06)	0.03	-0.05 (0.03)	0.08	-0.4	0.1	-0.2	0.05

4.7.7. Contribution of physical activity to metabolic disturbances in South Asians compared to Europeans

I used multiple regression to quantify the contribution of physical activity to metabolic disturbances amongst South Asians compared to Europeans (**table 4.12**). Results are expressed as difference in respective metabolic parameters amongst South Asians and Europeans, after adjustment for potential predictors. I found that glucose concentrations are 0.17mmol/L (SE:0.08, P=0.03) higher amongst South Asians than Europeans. After adjusting for moderate to vigorous or total physical activity, the difference in fasting glucose between South Asians and Europeans was reduced to up to 0.13mmol/L (SE:0.08) and was no longer statistically significant. In contrast, physical activity did not account for the differences in HOMA-IR and other glycaemic and lipid parameters between South Asians and Europeans (**table 4.12**).

Table 4.12 Contribution of physical activity towards the excess levels of metabolic disturbances amongst South Asians compared to Europeans. Beta coefficient from multiple linear regression represents the difference in metabolic parameters between South Asians (SA) and Europeans (EW) before and after adjustment for total physical activity (MET.minutes) per week.

Metabolic parameters	Unadjusted for physical activity	P	Adjusted for total MET.miunutes/week	P
Glucose	0.17 (0.08)	0.03	0.13 (0.08)	0.1
HbA1c	0.29 (0.05)	<0.001	0.27 (0.05)	<0.001
Insulin	3.61	<0.001	3.37	<0.001
HOMA-IR	1.29	<0.001	1.19	<0.001
Cholesterol	-0.2	0.03	-0.19	0.04
Triglycerides	0.23 (0.07)	0.002	0.2 (0.07)	0.006
HDL	-0.18	<0.001	-0.16	<0.001
LDL	-0.12	0.1	-0.12	0.2

4.8. Imputation of accelerometer data

Characteristics of participants in the discovery and replication groups are presented in **table 4.13**. There were no significant differences in age, physical and biochemical characteristics of participants in the two groups.

The proposed prediction models and associated R^2 for estimation of accelerometer MET.minutes in different physical activity categories, are presented in **table 4.14.** The prediction equations were then validated in the one-third replication group. Regression analysis of actual and predicted accelerometer data in the replication set showed a slope of 0.5 and 0.7 and intercept of 1.4 and 0.6 for total and moderate to vigorous physical activity prediction models respectively. In addition, the paired t-test showed that there was no mean difference between actual and predicted accelerometer MET.minutes in the cross-validation set. Prediction equations for the moderate to vigorous and total physical activity explained a variation of approximately 36% and 28% in the actual accelerometer data, respectively.

Table 4.13 Baseline clinical characteristics of participants in the discovery and replication group. Results are presented as mean (SD) or % for continuous and categorical data respectively. P values are from *independent student's t-test.*

	Discovery set Mean (SD)	**Cross-validation set Mean (SD)**	**p**
N	473	209	
Age (years)	57.67 (9.55)	56.37 (9.41)	0.1
Male (%)	49.7%	47.8%	0.7
Europeans (%)	26.4%	27.8%	0.7
Smoking status (%)			
Non-smoker	81.8%	83.7%	0.7
Ex-smoker	10.8%	8.6%	0.7
Current smoker	7.4%	7.7%	0.7
Family history of T2D (%)	24.9%	22.5%	0.5
History of T2D (%)	15.6%	12.4%	0.3
History of HTN (%)	33.4%	33.0%	0.9
Systolic BP (mmHg)	132.33 (16.84)	132.00 (18.47)	0.8
Diastolic BP (mmHg)	78.93 (9.82)	78.36 (10.50)	0.5
Height (cm)	164.80 (9.12)	165.36 (10.03)	0.5
Weight (cm)	75.31 (14.54)	75.18 (15.34)	0.9
Body mass index (kg/m^2)	27.63 (4.69)	27.37 (4.66)	0.5
Waist circumference (cm)	96.89 (11.80)	96.55 (11.93)	0.7
Hip circumference (cm)	103.04 (8.92)	101.89 (8.28)	0.1
Waist-hip ratio	0.94 (0.08)	0.94 (0.08)	0.3
Cholesterol (mmol/l)	5.03 (1.00)	5.02 (1.02)	0.9
Triglycerides (mmol/l)	1.39 (0.78)	1.38 (0.86)	0.9
HDL-C (mmol/l)	1.51 (0.44)	1.51 (0.45)	0.8
LDL-C(mmol/l)	2.89 (0.89)	2.90 (0.93)	0.9
Glucose (mmol/l)	5.75 (1.72)	5.66 (1.74)	0.5
HbA1c (%)	6.08 (1.10)	6.05 (1.04)	0.7

Table 4.14 Imputation models and associated R^2 for predicting accelerometer data (MET.minutes) in the LOLIPOP cohort study.

Physical activity measure	Prediction equation	R^2	Adjusted R^2
Light physical activity	0.8+(-0.01 x age) + (-0.08 x ethnicity) + (-0.03 x sex) + (-0.003 x systolic BP) + (0.004 x weight) + (-0.04 x waist) + (0.05 x cholesterol) + (0.02 x triglycerides) + (0.12 x LDL-C) + (0.19 x glucose) + (-0.06 x HbA1c) + (0.12 x T2D history) + (3.64 x WHR) + (0.04 x Hip circumference) + (-0.11 x smoking)	0.32	0.2
Moderate physical activity	-11.05 + (-0.03 x age) + (0.254 x sex) + (-0.12 x ethnicity) + (0.54 x T2D history) + (-0.18 x hypertension history) + (-0.07 x smoking) + (0.002 x systolic BP) + (0.06 x height) + (-0.02 x weight) + (0.09 x body-mass index) + (-0.08 x waist circumference) + (6.97 x WHR) + (0.07 x hip circumference) + (0.03 x triglycerides) + (-0.07 x LDL-C) + (-0.57 x glucose).	0.41	0.3
Vigorous physical activity	0.14 + (-0.03 x age) + (-0.28 x sex) + (-0.19 x race) + (-0.17 x coronary heart disease history) + (-0.26 x T2D history) + (-0.26 x hypertension history) + (0.02 x weight) + (0.02 x height) + (-0.08 x HbA1c).	0.32	0.3
Mod-vig physical activity	-9.67 + (-0.02 x age) + (0.20 x sex) + (-0.01 x ethnicity) + (0.58 x T2D history) + (0.17 x hypertension history) + (-0.65 x coronary heart disease) + (-0.08 x smoking status) + (0.01 x alcohol intake)+(-0.002 x systolic BP) + (0.05 x height) + (-0.02 x weight)+(0.08 x body-mass index) + (-0.08 x waist circumference) + (6.69 x WHR) + (0.06 x hip circumference) + (-0.02 x triglycerides) + (-0.09 x LDL-C) + (-0.67 x glucose).	0.50	0.4
Total physical activity	2.25 + (-0.01 x age) + (0.08 x sex) + (0.12 x race) + (0.31 x T2D history) + (-0.10 x hypertension history) + (-0.09 x smoking status) + (0.02 x height) + (0.02 x body-mass index) + (-0.01 x waist circumference) + (0.02 x triglycerides) + (-0.06 x LDL-C) + (-0.75 x glucose).	0.38	0.3

4.9. Discussion

My results show that total physical activity levels are ~31% lower amongst South Asians than Europeans in the UK. Total physical activity is independently and inversely associated with glucose and insulin resistance but not with other metabolic parameters. Low levels of physical activity do not account for the higher levels of insulin resistance amongst South Asians. However, lower physical activity levels amongst South Asians may contribute to their elevated glucose concentrations compared to Europeans. My results suggest that lifestyle modification through increased physical activity may help to improve glucose metabolism and thus reduce the excess burden of T2D amongst South Asians.

Though previous studies have suggested that levels of leisure time and total physical activity are lower amongst South Asians than Europeans, they have exclusively used semi-quantitative methods that are not validated amongst South Asians[12,200,259]. A recent study reported low levels of physical activity amongst South Asians compared to Europeans but was carried out in a population sample with low response rate (<5%) and exclusively male, and therefore unrepresentative of the UK South Asian population[260]. In the present study, I used a validated tri- axial accelerometer to quantify physical activity levels amongst a representative population sample of South Asian and European men and women recruited from general practitioner lists (response rates averaged 62% in South Asians and 61% in Europeans). I show that total physical activity levels are ~31% lower amongst South Asians than Europeans, as measured by energy expenditure during free living activity. Lower levels of physical activity amongst South Asians were most evident in the moderate and vigorous physical activity domains, but also present in light physical activity. Low levels of physical activity amongst South Asians were independent of and not explained by differences in age, sex or adiposity, compared to Europeans. My

results extend current knowledge by providing quantitative assessment of physical activity in a representative sample of South Asian men and women. The reasons underlying low levels of physical activity amongst South Asians are not known, but may include a lack of understanding regarding the health benefits associated with regular physical activity, as well as cultural expectations and barriers to participation in recreational activities, especially among South Asian women[247].

I did not find an association of physical activity with adiposity, triglycerides or HDL cholesterol concentrations. However, my results do show an association of lower levels of physical activity with higher insulin resistance and fasting glucose concentrations. In regression analysis, the relationship of physical activity with insulin resistance and glucose was not accounted for by differences in age, sex or adiposity, suggesting that physical activity has an independent effect on insulin resistance and fasting glucose concentrations. My results are consistent with published data which show that increased physical activity is associated with a reduction in insulin resistance and glucose concentrations in European populations[261-264]. My findings are consistent with experimental studies which show that physical activity stimulates translocation of GLUT4 glucose transporters, the rate-limiting step in glucose metabolism, in skeletal muscle[265].

My results show that insulin resistance, as measured by HOMA-IR, and related insulin and lipid disturbances are more common amongst South Asians than Europeans. Lower physical activity did not explain the presence of these metabolic abnormalities amongst South Asians. In contrast, I found that glucose concentrations were 0.17 mmol/L higher amongst South Asians than Europeans. After adjusting for total physical activity, the difference in glucose concentrations between the populations was lower and no longer statistically significant. My findings suggest that higher concentrations of glucose

amongst South Asians are in part accounted for by their lower levels of physical activity compared to Europeans. Abnormal glucose metabolism underlies T2D and impaired glucose tolerance, both major risk factors for cardiovascular disease. Prospective studies show that elevated glucose despite being in the normal range is a risk factor for cardiovascular disease[7,41]. Low physical activity amongst South Asians may therefore have a role in the increased risk of cardiovascular disease risk in this population, through an effect on glucose metabolism.

This is the first study to quantify physical activity levels using an objective, validated tool in a representative sample of South Asian and European men and women. However, my study does have some limitations. My study is cross-sectional rather than prospective and so may be susceptible to confounding effects ("reverse causation"). It is possible that my sample of participants may not be fully representative of the spectrum of South Asian and European populations. This is unlikely though as participants were recruited from general practitioner lists and showed the well-established patterns of insulin resistance and related metabolic abnormalities amongst South Asians. Modest sample size is a potential explanation for the failure to find the previously reported associations of physical activity with fasting insulin levels and related lipid abnormalities though this relationship is not consistently identified in other studies[266,267]. I also used HOMA-IR, a surrogate measure of insulin resistance, which is closely correlated with the gold standard Hyperinsulinaemic euglycaemic clamp but which remains a less accurate measure of insulin resistance. Finally, although accelerometers are an objective measure of physical activity and their use has been validated against the gold standard under close supervision, their accuracy in free living individuals is lower, and our estimates of physical activity may be imprecise.

In conclusion, I show that physical activity levels are lower amongst South Asians and may contribute to their increased fasting glucose concentrations, compared with Europeans. My results suggest the potential for increased physical activity to improve glucose metabolism and insulin resistance amongst South Asians, and help reduce their excess risk of T2D and cardiovascular disease.

Chapter 5: Physical activity and new-onset T2D in UK South Asians compared to Europeans.

5.1. Abstract

Background. Observational and interventional studies support a strong association between low physical activity levels and high incidence of T2D. Intervention studies conducted in patients with IGT suggest a preventive role of physical activity on the development and progression of T2D through both short and long term effects. Primary mechanism for this reduced risk is improvement in insulin sensitivity. The associations of physical activity with new-onset T2D has not been investigated in South Asians, a population with a higher prevalence of T2D compared to other ethnic groups including Europeans.

Methods. I used data from the ongoing LOLIPOP study comprising 17,606 South Asian and 7,766 European men and women. LOLIPOP participants are currently undergoing their ~9-year follow-up to identify cases of new-onset T2D. All participants completed a structured assessment of metabolic and cardiovascular health. I examined the relationship between physical activity levels (imputed accelerometer data, chapter 4) and increased risk of new-onset T2D amongst South Asians compared to Europeans. Linear and logistic regression analyses were used to determine the association between physical activity, new-onset T2D and associated metabolic parameters respectively.

Results. The incidence of new-onset T2D was 13.4% amongst South Asians and 4.6% amongst Europeans in the LOLIPOP cohort over mean 9 years' follow-up (P<0.001). Relative risk of T2D reduced by 3% with every 10% increase in total physical activity levels (P<0.001). The age, sex and adiposity adjusted relative risk of T2D in South Asians reduced from 2.8 (95%CI: 2.5-3.2, P=6.3 x 10^{-58}) to 2.3 (95% CI: 2.0-2.7, P=4.5 x 10^{-35}) after adjusting for physical activity levels. The T2D population attributable risk

(%) for achieving less than 600 MET.minutes per week was ~16% in South Asians and ~37% in Europeans. In addition, a 10% increase in total physical activity was associated with 4% decrease in HOMA-IR (P<0.001). Fasting glucose and insulin levels were reduced by 1% and 3% respectively, for every 10% increase in total physical activity levels. The relationships of physical activity with T2D, HOMA-IR and fasting glucose and insulin levels were not materially altered after adjusting for adiposity amongst both South Asians and Europeans.

Conclusion. My results confirm that risk of T2D is ~3 times higher in South Asians than in Europeans and this difference is not accounted by age, sex or adiposity. Low physical activity levels act as an independent risk factor in South Asians that may account for an important proportion of their increased T2D risk.

5.2. Aim

To study the contribution of physical activity levels to the risk of new-onset T2D and associated metabolic disturbances in South Asians and Europeans participating in the prospective LOLIPOP study.

5.2.1. Objectives

My objectives are to:

1. Determine the risk of T2D, pre-diabetes and associated metabolic disturbances in South Asians and Europeans.
2. Investigate the contribution of conventional risk factors to T2D amongst South Asians and Europeans.
3. Determine the relationship of physical activity with new-onset T2D and associated metabolic parameters amongst South Asians and Europeans.
4. Investigate the contribution of physical activity levels to the risk of new-onset T2D and associated metabolic disturbances.
5. Determine the population risk of T2D attributable to physical inactivity and South Asians and Europeans.

5.3. Background

The association of low physical activity levels with increased risk of type 2 diabetes (T2D) is well established. Results from various observational studies[268-270] and interventional studies[50,172,203,271] support a strong association between low physical activity levels and incidence of T2D. Intervention studies conducted in patients with impaired glucose tolerance (IGT) suggest a preventive role of physical activity on the development and progression of T2D through both short and long term effects[174]. The primary mechanism for this reduced risk is improvement in insulin sensitivity[175-178]. However, the associations of physical activity with new-onset T2D has not been investigated in South Asians, a population with a higher prevalence of T2D compared to other ethnic groups including Europeans.

South Asians are reported to be less physically active than their ethnic counterparts. In UK, documented physical activity levels amongst South Asians are 50–75% lower than those of Europeans[259]. Reduced levels of physical activity amongst South Asians may further increase the incidence of T2D in this population.

The incidence of T2D has been reported recently amongst UK South Asian and European men and women in west London. Results from the study showed that 1608 (11·9%) of 13 535 South Asians and 306 (4·3%) of 7066 Europeans had incident T2D over a mean of 8·5 years (SD 1·8) of follow-up. The age and sex adjusted risk of T2D was 3·1 times (95% CI 2·8–3·6; p<0·0001) higher amongst South Asians than Europeans. This risk difference remained 2·5 times (2·1–2·9; p<0·0001) higher even after adjustment for the major T2D risk factors[272]. Similar results were presented by

the Southall and Brent Revisited (SABRE) study which reported approximately 2.5-fold increased incidence of T2D amongst UK South Asians compared to Europeans[41].

The potential beneficial effects of physical activity in preventing T2D have been investigated in South Asians. Results from the Indian Diabetes Prevention Program (IDPP)[203] suggest that physical activity is as effective in the prevention of T2D amongst South Asians as is medical treatment and therefore physical activity can provide an efficient and cost effective mean for reducing and delaying the risk of T2D development amongst South Asians.

Few research studies that examined the association between physical activity levels and T2D among South Asians have been limited by small and non-representative sample sizes or cross-sectional design[273-275]. Therefore, the association of physical activity with incident T2D remains unidentified in this ethnic group. The aim of this study is to examine the association between levels of physical activity and incidence of T2D amongst UK South Asians.

5.4. Methods

5.4.1. Participants and setting

I used data from the ongoing LOLIPOP study to examine the relationship between physical activity and the increased risk of new-onset T2D amongst South Asians.

LOLIPOP is a prospective population based study comprising 17,606 South Asian and 7,766 European men and women, recruited at age 35-75 years from the

lists of 58 General Practitioners in West London, United Kingdom between 2001 and 2008. South Asians had all 4 grandparents born on the Indian subcontinent (India, Pakistan, Sri Lanka or Bangladesh). Europeans were of self-reported white ancestry.

At baseline, all participants completed a structured assessment of metabolic and cardiovascular health, including personal and family history, and anthropometric measurements. Blood samples were collected for complete blood count and measurement of fasting glucose, insulin, HbA1c and lipid profile. T2D was defined as physician diagnosis, fasting glucose ≥7mmol/L or HbA1c ≥6.5%. Physical activity was quantified using the Leisure time physical activity questionnaire (LPAQ).

LOLIPOP participants are currently undergoing their ~9-year follow-up to identify cases of new-onset T2D. Follow-up is carried out using the electronic health records from primary care practitioners. Health records are extracted for each participant, and structured questions used to identify individuals with new-onset T2D. In addition, 7,640 participants have attended clinical evaluation, including questionnaire and fasting blood samples for glucose and HbA1c, enabling identification of people confirmed to be free from T2D at the end of follow-up (not on treatment for T2D and fasting glucose <7mmol/L and HbA1c <6.5%). Incident T2D cases are defined as free from T2D at baseline, but who develop T2D during follow-up. Controls are free from T2D both at baseline and follow-up.

Clinical follow up of the men and women participating in the LOLIPOP study

All participants in the LOLIPOP study were re-invited for assessment over the five years between 2008 and 2012. Participants were invited by post to attend an appointment at LOLIPOP research clinics, located at Ealing Hospital.

Invitations started with those recruited earliest and worked sequentially through the cohort. Up to three invitations were sent by post, at monthly intervals. NHS number is recorded for all but 13 of the LOLIPOP participants and was used for tracking. The local Primary Care Trusts provide regular updates of the addresses of participants still resident in the area, and 96% of participants were still registered with one of the collaborating LOLIPOP GPs. Persons who moved out of area were located through the NHS tracing service, and invited to attend the LOLIPOP follow-up clinic.

5.4.2. Clinical characterisation

Participants attended the research clinic following an overnight fast. Data on medical history, family history, current medications, personal and social history was collected using an interview-administered questionnaire.

5.4.3. Physical assessment

Weight, height, waist circumference, hip circumference and blood pressure were measured using standardised protocols. Weight was measured to the nearest 0.1kg using digital scales mounted on a hard and flat surface. Height, waist and hip circumference were measured to the nearest 0.1cm. Height was measured using a stadiometer, mounted on a hard and flat surface. Waist circumference was defined as the point midway between the iliac crest and lowest rib. Hip circumference was defined

as the maximum circumference over the greater trochanters and buttocks. Blood pressure was measured using an OMRON 705CP blood pressure monitor. Three measurements were taken and an average of these was documented.

5.4.4. Biochemical assessment

Fasting venous blood samples were collected for glucose, insulin, lipid profile, urea, electrolytes and HbA1c. Insulin resistance was assessed using the homeostatic model assessment (HOMA- IR), where HOMA-IR = [Glucose (mmol/L) x Insulin (mU/L)] / 22.5.

5.4.5. Leisure-time physical activity questionnaire

Physical activity levels were measured amongst all participants using the LPAQ. Leisure time physical activity was classified as light, moderate or vigorous according to the CDC classification scheme (USA). Results are presented as the estimation of physical activity energy expenditure in MET.minutes/week by multiplying minutes spent in that activity with MET value of activity intensity (a MET value of 4 and 8 for moderate and vigorous physical activity, respectively). An individual was defined as physically active when he achieves 600 MET.minutes of moderate to vigorous physical activity per week.

5.4.6. Objective measure of physical activity levels

I used physical activity data measured objectively using Actigraph GT3X+ accelerometer, amongst 682 LOLIPOP participants, to impute the accelerometer data amongst all LOLIPOP participants (method and results have been described in **chapter 4**). Multiple linear regression was used to develop prediction equations for

estimation of physical activity as measured by accelerometer amongst South Asians and Europeans. An imputation function was developed using the Actigraph GT3X+ accelerometer data as the outcome measure. The imputation model included demographic (ethnicity, sex, age, and family history of type 2 diabetes, hypertension and coronary heart disease), anthropometric (weight, height, body mass index, waist-hip ratio and waist and hip circumference) and biochemical measures (fasting glucose, HbA1c, cholesterol, triglycerides, LDL-C and HDL-C) as potential predictors. I used the imputed accelerometer data to determine the contribution of objective physical activity to new-onset T2D and associated metabolic disturbances amongst South Asians and Europeans.

5.5. Statistical analysis

Statistical analyses were performed using SPSS 23. Continuous data were presented as mean ± standard deviation (SD), and categorical data as percentage (%). Distribution of study variables were assessed using histograms and logarithmic transformation of positively skewed data (glucose, insulin, HOMA-IR and physical activity measures) was carried out to restore a normal distribution.

Initially, I carried out univariate analysis to investigate differences between South Asians and Europeans using the independent samples t-test and chi squared test for continuous and categorical variables respectively. P value <0.05 was considered statistically significant.

Power

Follow-up was started in Q1 2008 and T2D events were censored at Dec 31st, 2015, allowing 150,000 person years of follow-up, (average of 7 years for each of 15,000 persons who attended the LOLIPOP clinics). Based on national data ([www.heartstats.org] and the HES database), and taking into account loss-to-follow-up, withdrawal and healthy cohort effect, we estimated a total of ~2080 T2D events. This affords 95% power to detect with odds ratio for T2D of 1.4, 1.3 and 1.25 for exposure with 10%, 20% and 30% population prevalence respectively, $P<0.05$.

5.5.1. Effect of physical activity on T2D, insulin resistance and glucose

Regression analysis was used to determine the effect of physical activity on T2D and associated metabolic disturbances. Positively skewed outcome variables (glucose, insulin, and HOMA-IR) and the predictors (physical activity measure) were log transformed to restore normal distribution.

Logistic regression was carried out to determine the effect of physical activity on T2D incidence. Confounding variables including age, sex and ethnicity were controlled by stratification. Meta-analysis was performed to obtain the average effect size. The average effect size represented the relative risk of new-onset T2D for 10-fold increase in physical activity levels.

Linear regression analysis was used to determine the association of physical activity (questionnaire and imputed accelerometer MET.minutes) with glucose, insulin and HOMA IR. Age, sex and ethnicity were controlled by stratification and meta-analysis was performed to obtain average effect size. Beta coefficient from linear

regression represents the percentage change in the outcome variable with every 1% change in physical activity measure.

5.5.2. T2D Population attributable risk (%) for physical inactivity

To calculate the magnitude of T2D risk attributable to low physical activity levels in South Asians compared with Europeans, I estimated the T2D population attributable risk within each ethnic group using the standard methodology. This was calculated as *Pe (RR-1) x 100/Pe (RR-1) + 1,* where RR is the relative risk (estimated as the OR from logistic regression) and Pe is the proportion of population exposed to physical activity levels below the threshold; 600MET.minutes per week was the primary threshold to define physical inactivity, based on national recommendations, but as sensitivity analyses I used a range of alternate thresholds (450, 750 and 1000 MET.minutes per week).

5.6. Results

5.6.1. Comparison of baseline characteristics of participants who were lost to follow up with those who were followed up.

Table 5.1 shows that respondents (participants who came for the follow up) were younger, and had lower prevalence of metabolic disturbances than those who did not participate (all $p<0.01$). Compared with non-participants, respondents were also more likely to be physically active. Overall, the respondents were healthier than the non-respondents.

Table 5.1 Baseline characteristics of European and South Asian participants who were lost to follow up compared to those who were followed up.

	Europeans			South Asians		
Follow-up	**No**	**Yes**	**p**	**No**	**Yes**	**p**
N	**5381**	**3837**		**11906**	**11108**	
Age (years)	53 (12.2)	52.4 (11.2)	0.03	50.7 (12.2)	50.9 (10.9)	0.1
Male (%)	63.1%	61.3%	0.07	61.4%	64.5%	<0.001
Coronary heart disease (%)	6.6%	4.4%	<0.001	11.4%	9.7%	<0.001
Hypertension (%)	23.7%	17.8%	<0.001	31.0%	29.2%	0.004
Type 2 diabetes (%)	9.3%	5.4%	<0.001	21.7%	16.7%	<0.001
Vigorous physical activity (min/week)	7.9 (38.8)	10.8 (47.4)	0.002	5.6 (31.1)	5.5 (30.4)	0.9
Moderate physical activity (min/week)	54.2 (79.8)	62.4 (80.5)	<0.001	30.2 (60.7)	33.1 (64.1)	0.001
Systolic blood pressure (mm Hg)	132.6 (20)	130.1 (18.7)	<0.001	131.8 (20.6)	131 (19.1)	0.003
Diastolic blood pressure (mm Hg)	80 (10.9)	79.4 (10.5)	0.01	80.2 (11.3)	80.6 (10.7)	0.004
Height (cm)	170.1 (9.8)	170.7 (9.5)	0.003	164.9 (9.8)	165.7 (9.4)	<0.001
Weight (cm)	80.2 (17.8)	79.4 (16.1)	0.01	74.5 (14.8)	74.5 (13.7)	0.8
BMI (kg/m2)	27.7 (5.5)	27.2 (4.8)	<0.001	27.4 (4.9)	27.1 (4.3)	<0.001
Waist circumference (cm)	96 (14.4)	94.2 (13.2)	<0.001	96.6 (12.3)	96 (11.2)	0.001
Hip circumference (cm)	103.5 (10.4)	102.9 (9)	0.005	101.6 (9.2)	101.3 (8.3)	0.007
Waist hip ratio	0.92 (0.09)	0.91 (0.08)	<0.001	0.95 (0.08)	0.94 (0.07)	0.02
Cholesterol (mmol/l)	5.4 (1.1)	5.5 (1.1)	0.09	5.2 (1.1)	5.2 (1.1)	0.004
Triglycerides (mmol/l)	1.5 (1.2)	1.4 (1)	<0.001	1.7 (1.2)	1.7 (1.1)	0.3
HDL-cholesterol (mmol/l)	1.41 (0.38)	1.44 (0.37)	0.002	1.27 (0.31)	1.27 (0.30)	0.1
LDL-cholesterol (mmol/l)	3.3 (0.9)	3.4 (0.9)	0.002	3.2 (0.9)	3.2 (0.9)	<0.001
Glucose (mmol/l)	5.5 (1.8)	5.3 (1.3)	<0.001	5.9 (2.2)	5.7 (1.8)	<0.001
Insulin (mmol/l)	10.4 (10.4)	9.3 (9.6)	<0.001	13.6 (12.5)	12.7 (11.7)	<0.001

5.6.2. T2D and pre-diabetes amongst South Asians and Europeans

Clinical characteristics of LOLIPOP study participants are shown in **tables 5.2 and 5.3**. Mean prevalence of T2D was 21.1% among South Asians and 7.3% among Europeans. Higher rates of T2D were present in South Asians than Europeans in both men and women **(figures 5.1)**. After adjustment for age and sex, the odds ratio for T2D was 3.3 (95% CI: 2.9 – 3.7, P<0.001) amongst South Asians compared to Europeans (**table 5.4**). Odds ratio for T2D in South Asians compared to Europeans was higher in younger age groups (**table 5.5**). The mean prevalence of pre-diabetes was 27.8% amongst South Asians, compared to 13.6% in Europeans (P<0.001). Similar results were observed in both men and women (**table 5.2 and figure 5.2**)

Table 5.2 Baseline characteristics of the South Asians and Europeans free from T2D at enrolment to the LOLIPOP study. Results are presented as mean (SD) or as % for continuous and categorical data respectively.

	Europeans	**South Asians**	**P**
N	7,066	13,535	
Follow-up (yrs)	8.8 (1.7)	8.4 (1.7)	0.94
New onset T2D	4.6%	13.4%	$3.3x10^{-59}$
Age (yrs)	52.2 (11.4)	49.1 (10.9)	$1.9x10^{-81}$
Male (%)	61.2%	60.4%	0.12
Family history of T2D	17.8%	36.1%	$5.9x10^{-163}$
Physical activity (%)	60%	48%	$9.3x10^{-178}$
Leisure time physical activity			
Moderate physical activity (MET.minutes)	243.8 (327.5)	132.9 (257.7)	$1.1x10^{-124}$
Vigorous physical activity (MET.minutes)	80.9 (359.0)	47.5 (264.4)	$2.5x10^{-11}$
Total physical activity (MET.minutes)	324.6 (497.1)	180.4 (380.7)	$7.9x10^{-96}$
Impaired fasting glucose (%)	6.0%	6.4%	0.28
Fasting glucose (mmol/L)	5.07 (0.52)	5.09 (0.52)	$5.4x10^{-3}$
HbA1c (%)	5.29 (0.43)	5.53 (0.45)	$5.8x10^{-269}$
Insulin (IU/L)	9.2 (7.8)	11.9 (8.7)	$3.5x10^{-90}$
HOMA-IR	2.2 (2.0)	2.8 (2.2)	$2.4x10^{-77}$
HOMA-B	120 (207)	156 (115)	$1.2x10^{-66}$
Body mass index (kg/m^2)	27.2 (4.9)	27.0 (4.4)	$1.2x10^{-2}$
Waist circumference (cm)	94.3 (13.3)	95.1 (11.4)	$1.9x10^{-6}$
Waist-hip ratio	0.94 (0.07)	0.97 (0.07	$3.3x10^{-98}$
Treated hypertension (%)	18.6%	21.7%	$1.2x10^{-7}$
Systolic BP (mmHg)	130.4 (19.1)	128.7 (18.7)	$2.3x10^{-10}$
Diastolic BP (mmHg)	79.4 (10.6)	80.0 (10.8)	$7.3x10^{-5}$
Cholesterol (mmol/L)	5.42 (1.09)	5.29 (1.04)	$1.8x10^{-17}$
Triglycerides (mmol/L)	1.44 (1.06)	1.60 (1.08)	$1.2x10^{-24}$
HDL cholesterol (mmol/L)	1.44 (0.38)	1.30 (0.32)	$1.0x10^{-170}$
Smoking (%)			
Never smoked	42.2%	81.8%	$1.6x10^{-6}$
Ex-smoker	32.1%	8.1%	$2.1x10^{-5}$
Current smoker	25.7%	10.2%	$1.2x10^{-5}$

Table 5.3 Baseline clinical characteristics of new-onset T2D cases and controls in the LOLIPOP cohort study. Results are presented as mean (SD) or % for continuous and categorical data respectively. P values are for comparison of T2D cases and controls in the respective ethnic groups.

	Europeans			South Asians		
	Controls	**Incident T2D**	**P**	**Controls**	**Incident T2D**	**P**
N	5560	327		10,504	1,796	
Age (yrs)	51.8±11.2	58.9±9.5	$1.3x10^{-26}$	48.7±10.8	52.2±10.0	$3.3x10^{-36}$
Male (%)	58.8	75.2	$1.3x10^{-8}$	57.9	67.3	$7.9x10^{-13}$
Family history T2D (%)	17.7	23.2	0.01	35.2	43.0	$2.4x10^{-9}$
Leisure time physical activity						
Physically active (%)	52.9	39.9	$8.3x10^{-6}$	32.5	26.2	$4.5x10^{-7}$
Moderate physical activity (MET.min)	247.9±329.7	187.7±313.0	0.001	139.6±262.3	112.9±241.9	$2.1x10^{-5}$
Vigorous physical activity (MET.min)	80.5±350.4	45.3±244.0	0.01	50.9±272.3	35.5±248.7	0.02
Total physical activity (MET.min)	328.3±494.7	232.9±418.8	$8.9x10^{-5}$	190.4±391.2	148.4±352.7	$4.7x10^{-6}$
Body mass index (kg/m^2)	27.0±4.8	31.1±5.4	$2.9x10^{-47}$	26.8±4.3	28.9±4.6	$3.0x10^{-76}$
Waist (cm)	93.5±13.0	105.6±13.0	$3.9x10^{-55}$	94.1±11.1	100.5±11.2	$1.1x10^{-107}$
Waist-hip ratio	0.91±0.08	0.97±0.07	$1.5x10^{-40}$	0.93±0.08	0.97±0.07	$5.9x10^{-86}$
Glucose (mmol/L)	5.0±0.5	5.7±0.6	$8.9x10^{-104}$	5.0±0.5	5.5±0.6	$1.3x10^{-209}$
Insulin (IU/L)	8.8±7.4	15.5±10.7	$3.2x10^{-45}$	11.2±8.2	16.0±10.4	$2.4x10^{-64}$
HbA1c (%)	5.3±0.4	5.6±0.5	$3.7x10^{-42}$	5.5±0.4	5.8±0.5	$1.8x10^{-139}$
HOMA-IR	2.1±1.9	4.1±3.1	$4.9x10^{-62}$	2.5±2.0	3.9±2.8	$7.8x10^{-80}$
Impaired fasting glucose (%)	4.1	33.0	$1.3x10^{-26}$	3.4	24.1	$1.3x10^{-26}$

Table 5.4 Odds ratio (95% CI) for T2D amongst South Asians versus Europeans, overall and stratified by sex. Results are from age adjusted logistic regression analysis.

	OR of T2D in SA vs. EW (95% CI)	P
Overall	3.3 (2.9-3.7)	<0.001
Males	3.0 (2.6-3.5)	<0.001
Females	3.9 (3.1-4.9)	<0.001

Table 5.5 Odds ratio (95% CI) for T2D amongst South Asians versus Europeans stratified by age. Results are from sex adjusted logistic regression analysis.

Age group (years)	OR of T2D in SA vs. EW (95% CI)	P
35-44	6.1 (4.2-8.9)	<0.001
45-54	3.9 (3.1-4.9)	<0.001
55-64	3.0 (2.5-3.7)	<0.001
>65	1.9 (1.5-2.5)	<0.001

Figure 5.1 Prevalence of T2D amongst South Asians and Europeans (overall and stratified by sex). Results were compared between South Asians and Europeans using chi-square test. P value for all comparisons was <0.001.

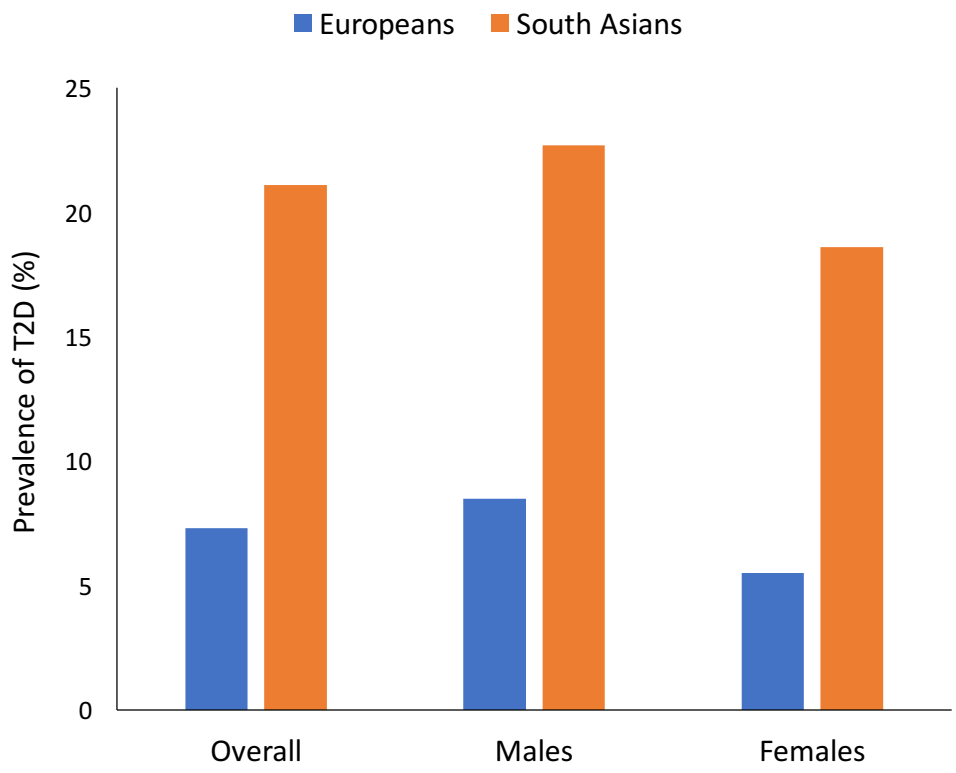
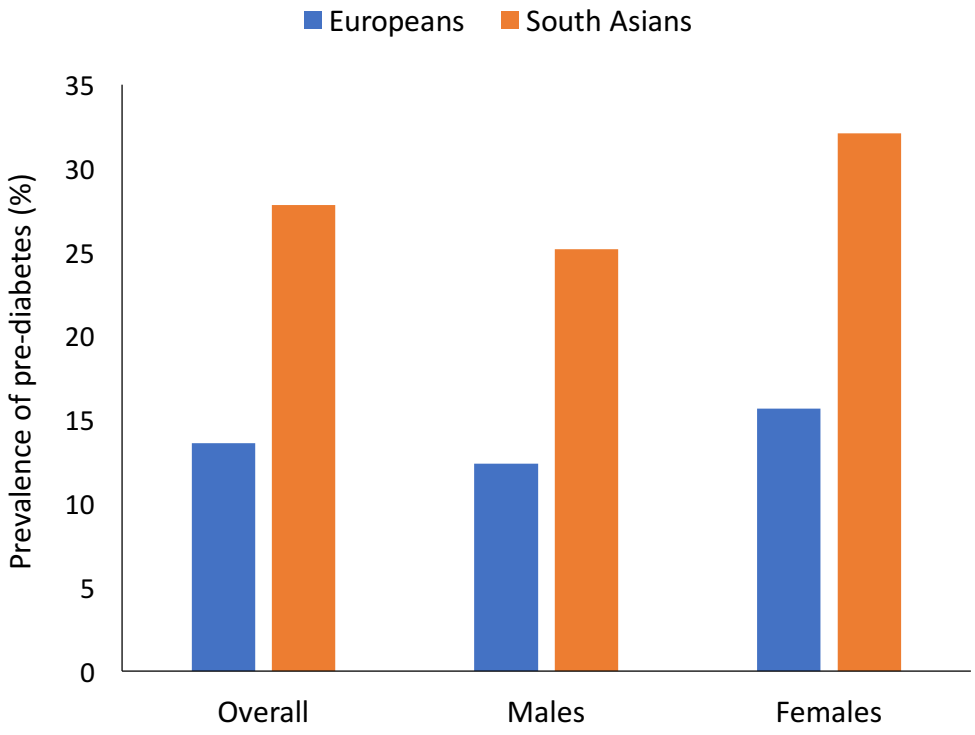


Figure 5.2 Prevalence of Pre-diabetes amongst South Asians and Europeans (overall and stratified by sex). Results were compared between South Asians and Europeans using chi-square test. P value for all comparisons was <0.001. Pre-diabetes was defined, according to the ADA classification, as plasma HbA1c >5.7% and <6.5%.



After completion of follow-up, 1,786 South Asians and 327 Europeans with new-onset T2D were identified. The incidence of new-onset T2D was 13.4% amongst South Asians and 4.6% amongst Europeans in the LOLIPOP cohort over mean 9 years' follow-up. Higher rates of T2D were present in South Asians than Europeans in both men and women (**figure 5.3 and figure 5.4**)

Figure 5.3 Incidence of T2D, over a follow up period of 9 years, amongst South Asians and Europeans stratified by age. Error bars represent the 95% CI. Results were compared between South Asians and Europeans using chi-square test. P value for all comparisons was <0.001.

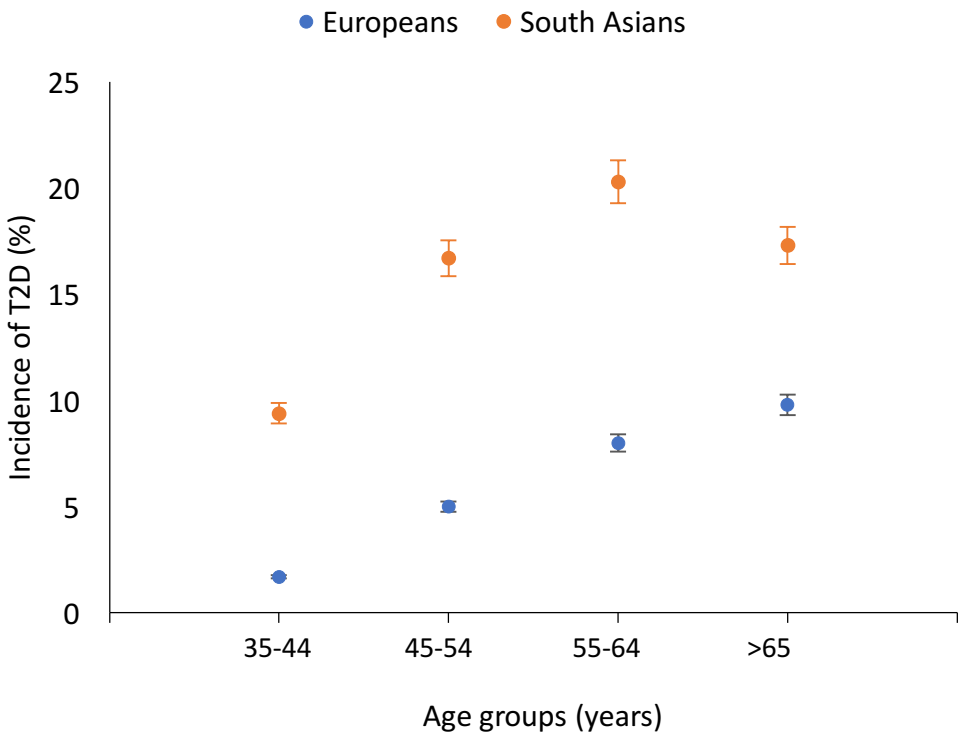
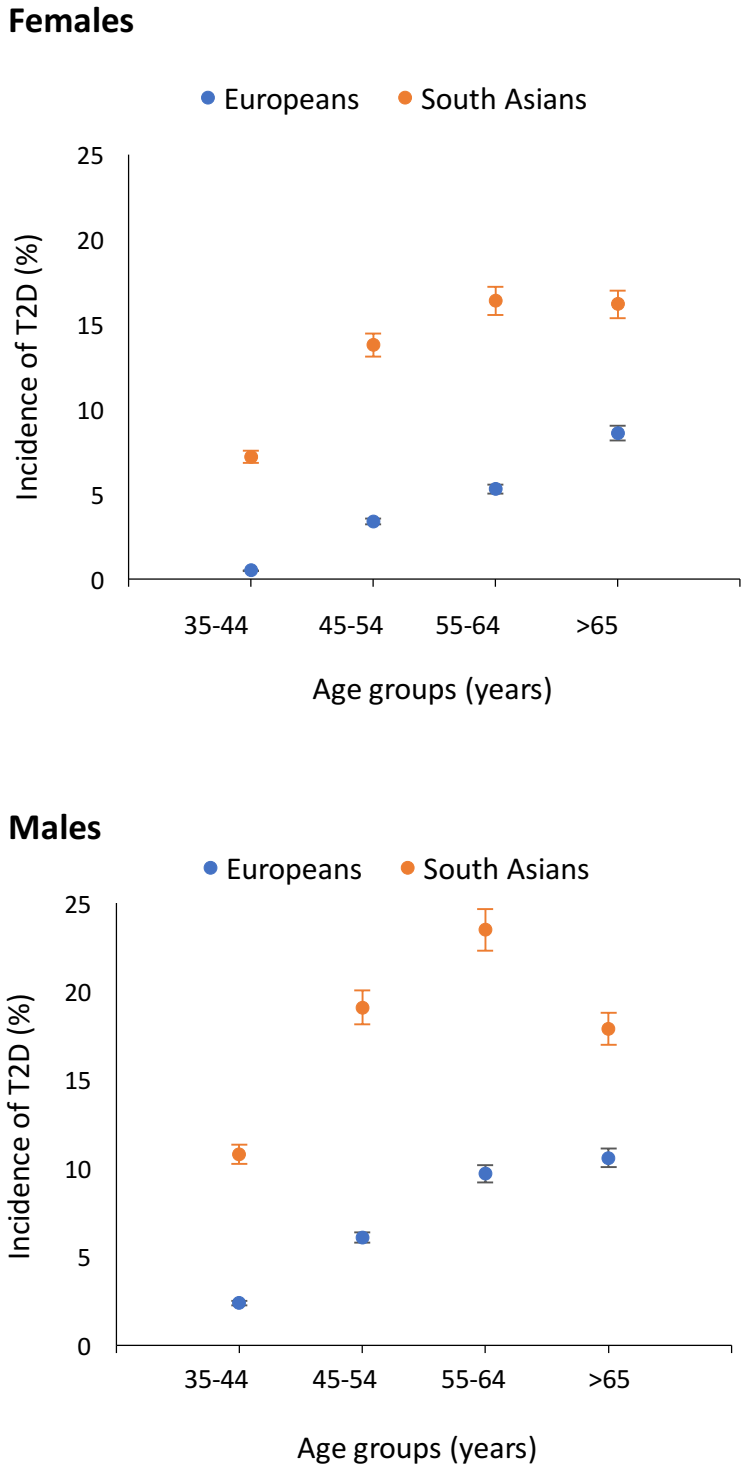


Figure 5.4 Age and sex stratified incidence of T2D, over a follow up period of 9 years, amongst South Asians and Europeans stratified by age. Error bars represent the 95% CI. Results were compared between South Asians and Europeans using chi-square test. P value for all comparisons was <0.001.



5.6.3. HOMA-IR and associated metabolic parameters amongst South Asians and Europeans

At baseline, South Asians had greater levels of metabolic disturbances compared to Europeans **(table 5.2)**. HOMA-IR, fasting glucose and fasting insulin levels were 24%, 39% and 26% higher in South Asians than in Europeans, respectively (all P<0.0001). South Asians had higher waist circumference, waist-hip-ratio, HbA1c and triglycerides, and lower HDL cholesterol, compared to Europeans (all P<0.001).

5.6.4. Contribution of conventional risk factors to T2D amongst South Asians compared to Europeans

Participants who developed T2D during the 9-year follow-up had higher baseline metabolic disturbances, which predict T2D, compared to controls in both South Asians and Europeans (**table 5.3**). Non-modifiable risk factors like age, sex and family history of T2D were higher in participants with incident T2D than in controls at baseline (all P<0.0001). In addition, controls in both populations had lower levels of adiposity (body mass index, waist circumference and waist hip ratio, all P<0.0001), insulin resistance and associated glycaemic parameters compared to participants who developed T2D during the follow-up (all P<0.0001).

I investigated the contribution of adiposity to the higher risk of T2D in South Asians compared to Europeans. In logistic regression body mass index, waist hip ratio and waist circumference were associated with an increased risk of T2D, in both South Asians and Europeans, though the effect size for waist hip ratio and waist circumference was lower in South Asians than Europeans (P=0.003 and P=0.007 for

waist hip ratio*ethnicity and waist circumference*ethnicity interaction respectively) (**table 5.6**). An increase of 1SD in adiposity, as assessed by body mass index, waist hip ratio and waist circumference, was associated with ~1.5 to 2-fold increase in the risk of T2D amongst the two populations, after adjusting for age and sex. South Asians had ~3-fold higher risk of T2D compared to Europeans (unadjusted for adiposity). This risk difference remained the same even after adjustment for body mass index, waist hip ratio and waist circumference. Hence, the ~3-fold higher rate of T2D in South Asians compared to Europeans was not accounted for by the difference in adiposity measures between the two populations (**table 5.7**).

5.6.5. Physical activity levels amongst South Asians and Europeans

South Asians performed ~30% lower levels of total physical activity per week than Europeans (P<0.001) **(figure 5.5 and 5.6)**. Physical activity levels in all intensity domains (light, moderate, vigorous, and moderate to vigorous) were lower in South Asians than in Europeans in each age group (**figure 5.7**). The proportion of physically active (individuals achieving 600 MET.minutes/week of moderate to vigorous physical activity) South Asians was significantly less compared to Europeans (48% vs. 60%, P<0.001). Lower levels of physical activity amongst South Asians compared to Europeans were present in both men and women, and was more prominent in younger age groups (P<0.001 for Age*ethnicity interaction). Compared to South Asians and European participants who developed T2D on follow-up**,** both South Asian and European controls performed higher levels of physical activity in all intensity domains (P<0.0001) compared to T2D cases in both populations (**table 5.3**).

Table 5.6 Age and sex adjusted logistic regression analysis for association of adiposity with T2D risk amongst South Asians and Europeans. Odds ratio (95% CI) are presented for one standard deviation change in the predictor variable.

	Europeans		South Asians	
	OR (95% CI) for T2D	**P**	**OR (95% CI) for T2D**	**P**
Age	1.9 (1.6-2.1)	<0.001	1.4 (1.3-1.5)	<0.001
Body mass index	2.0 (1.8-2.2)	<0.001	1.7 (1.6-1.8)	<0.001
Waist hip ratio	1.9 (1.7-2.2)	<0.001	1.6 (1.5-1.7)	<0.001
Waist circumference	2.2 (2.0-2.5)	<0.001	1.7 (1.6-1.8)	<0.001

Table 5.7 Age and sex adjusted logistic regression analysis for determining the contribution of adiposity to the difference in risk of T2D amongst South Asians and Europeans. Odds ratio (95% CI) present the odds of T2D in South Asians compared to Europeans after adjusting for the predictor variable.

	OR (95% CI) of T2D in SA vs. EW	**P**
Age	3.3 (2.9-3.7)	<0.001
Body mass index	3.3 (2.9-3.7)	<0.001
Waist hip ratio	2.8 (2.5-3.2)	<0.001
Waist circumference	3.2 (2.8-3.6)	<0.001

Figure 5.5 Age stratified levels of total physical activity (MET.minutes/week) amongst South Asians and Europeans. Error bars represent 95% CI. Results in each age group were compared between South Asians and Europeans using independent student t-test. P value for all comparisons was <0.001.

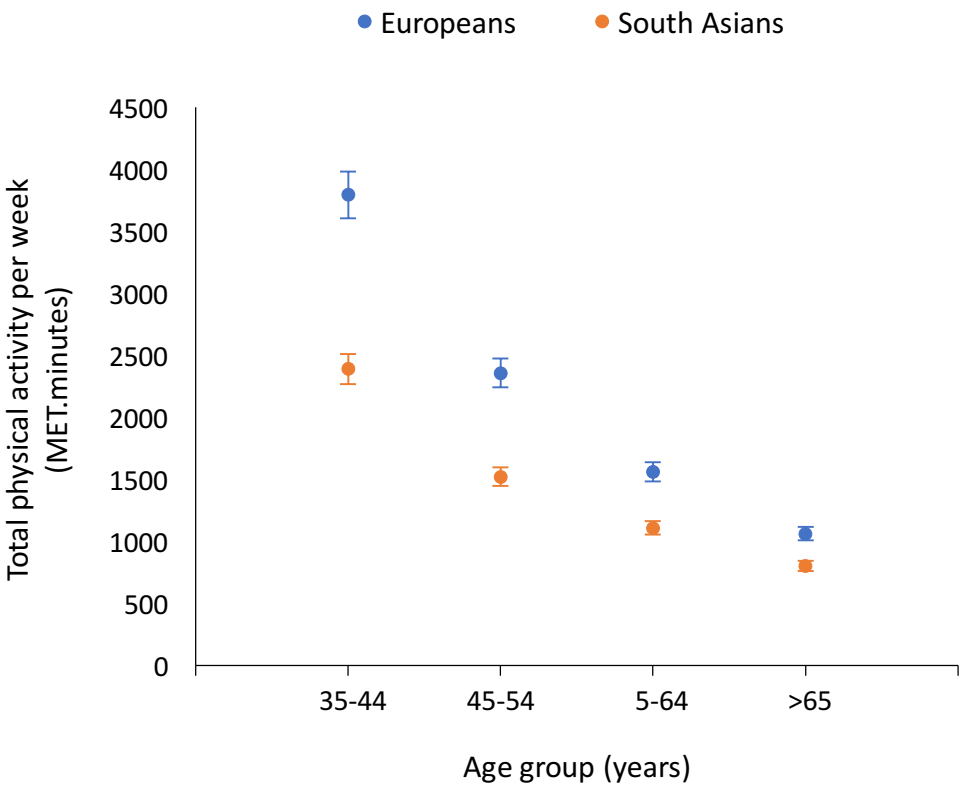


Figure 5.6 Age stratified levels of total physical activity (MET.minutes/week) amongst South Asian and European men and women. Error bars represent 95% CI. Results in each age group were compared between South Asian and European men and women using independent student t-test. P value for all comparisons was <0.001.

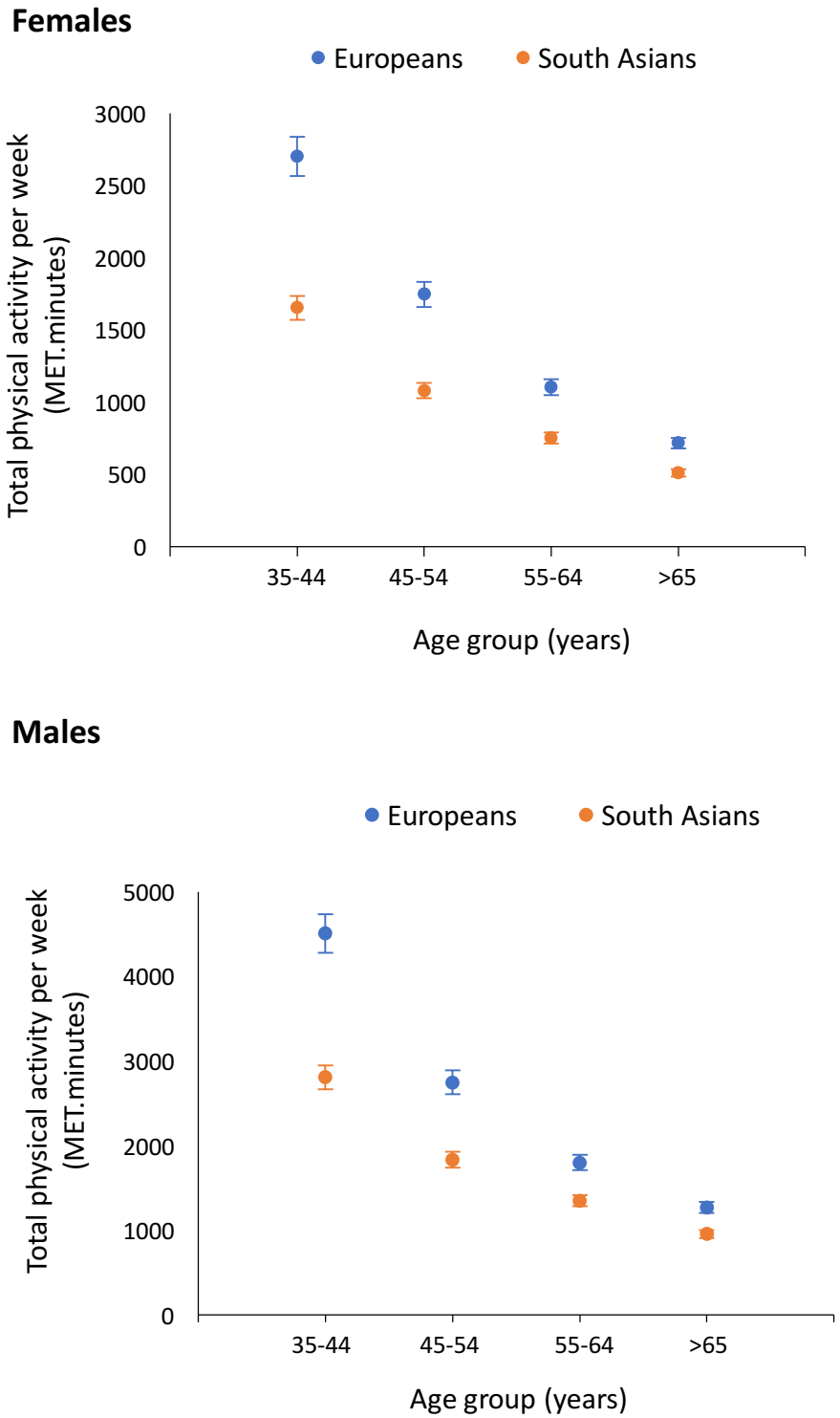
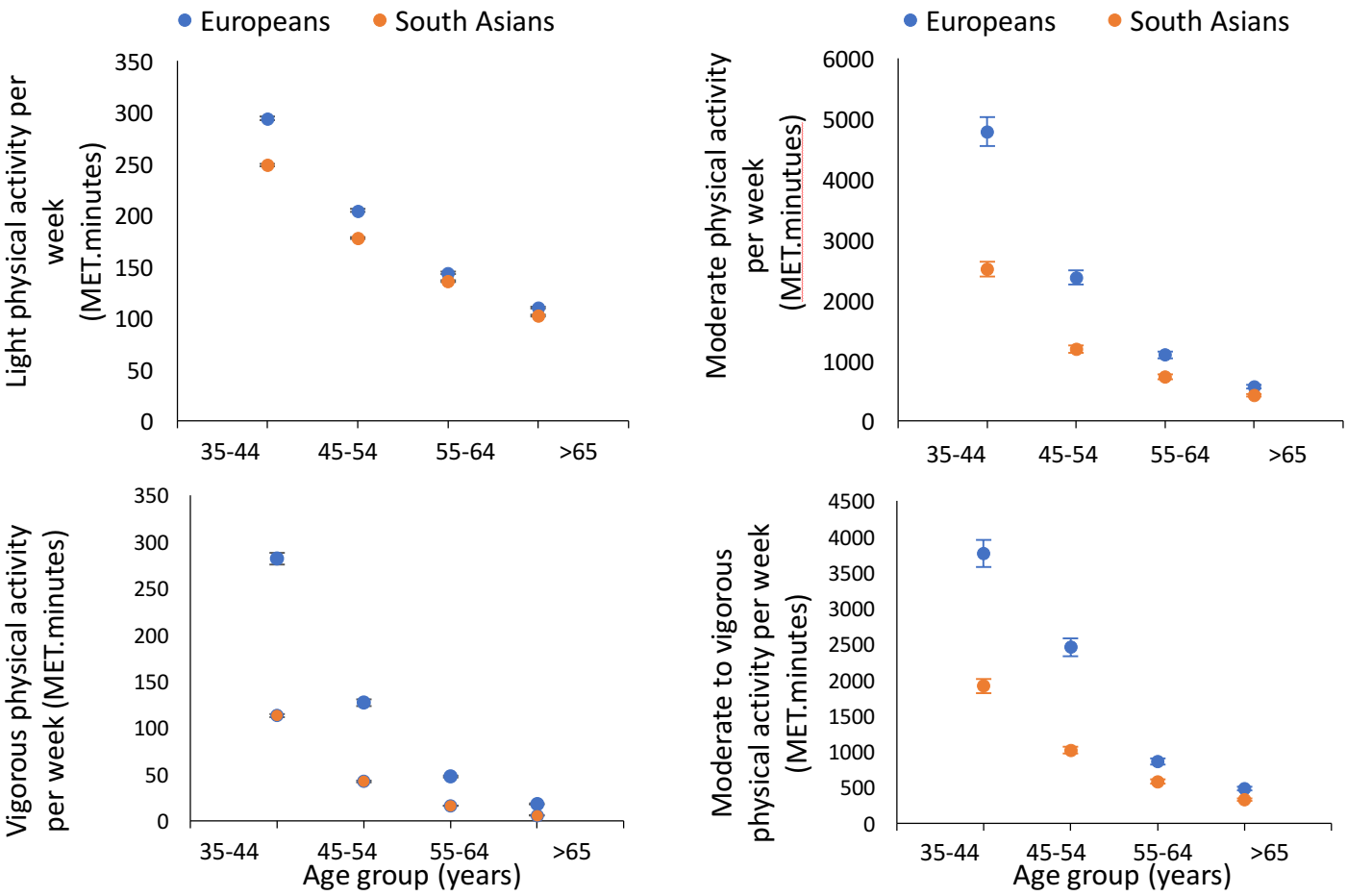


Figure 5.7 Age stratified levels of physical activity (MET.minutes/week) amongst South Asians and Europeans in pre-specified intensity domains (light, moderate, vigorous and moderate to vigorous physical activity). Error bars represent 95% CI. Results in each age group were compared between South Asians and Europeans using independent student t-test. P value for all comparisons was <0.001.



5.6.6. Physical activity and risk of T2D

The association of physical activity levels with the risk of T2D was determined using logistic regression (**table 5.8**). Results are presented as the relative risk of T2D with every 10% increase in physical activity levels (MET.minutes/week). In all study participants, a 10% increase in total physical activity per week was associated with 3% (95% CI: 2.5 – 3.2, P<0.001) reduction in the risk of T2D. Analysis for each ethnic group revealed a similar association of physical activity with the risk of new-onset T2D. Amongst Europeans, however, the decrease in risk of T2D was 1% higher than amongst South Asians for a 10% increase in total physical activity levels (P_{het}: 0.04, **table 5.8**). Similar associations were observed between moderate to vigorous physical activity levels and risk of T2D (**table 5.8**). The association of physical activity levels and risk of T2D was independent of adiposity (**table 5.9**).

I determined the incidence of T2D in quartiles of total physical activity per week amongst both South Asians and Europeans. Incidence of T2D in both South Asians and Europeans was greatest in the least physically active quartile (1^{st} quartile: ~20% and 10% respectively) and lowest in the most physically active quartile (4^{th} quartile: ~7% and 2% respectively). Comparing South Asians to Europeans, rates of new-onset T2D were higher in the former at every level of physical activity (all P<0.001) **(figure 5.8).**

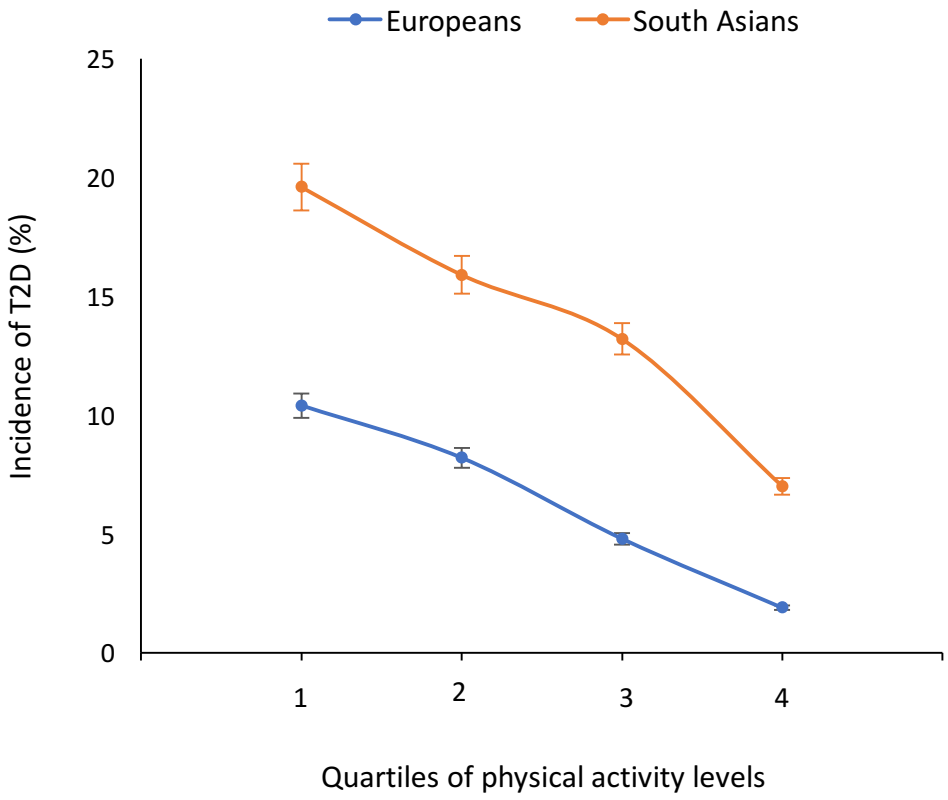
Table 5.8 Association of physical activity (MET.minutes/week) with new-onset T2D in participants of LOLIPOP cohort study. South Asians and Europeans. Results are presented as relative risk (95% CI) of new-onset T2D for every 10% increase in of physical activity levels (MET.minutes/week). P_{het} is for comparison of results between Europeans and South Asians.

	All participants		Europeans		South Asians		Phet
	RR (95% CI)	**P**	**RR (95% CI)**	**P**	**RR (95% CI)**	**P**	
MET.minutes per week							
Total physical activity	0.97 (0.96-0.98)	$2.2x10^{-62}$	0.96 (0.95-0.97)	$5.3x10^{-20}$	0.97 (0.96-0.98)	$5.6x10^{-45}$	0.04
Moderate to vigorous physical activity	0.99 (0.98-0.99)	$4.6x10^{-43}$	0.0.98 (0.98-0.99)	$4.3x10^{-20}$	0.99 (0.99-0.99)	$8.0x10^{-27}$	0.002

Table 5.9 Association of physical activity (MET.minutes/week) with new-onset T2D in participants of LOLIPOP cohort study, after adjusting for adiposity (BMI and WHR). South Asians and Europeans. Results are presented as relative risk (95% CI) of new-onset T2D for every 10% increase in of physical activity levels (MET.minutes/week).

	Incident T2D	
	RR (95% CI)	**p**
MET.minutes per week		
Total physical activity	0.97 (0.96 - 0.97)	$6.9x10^{-76}$
Moderate to vigorous physical activity	0.99 (0.98 - 0.99)	$4.7x10^{-48}$

Figure 5.8 Incidence of T2D (mean, 95% confidence intervals) amongst South Asians and Europeans across quartiles of physical activity levels per week. Chi-squared test was used to compare incidence of T2D between South Asians and Europeans; $p<0.001$ at each physical activity category.



5.6.7. Physical activity and risk of T2D associated metabolic disturbances

I investigated the association of physical activity levels (MET.minutes/week) with HOMA-IR and fasting glucose and insulin levels using linear regression analysis (**table 5.10**). Physical activity levels were inversely associated with HOMA-IR, fasting glucose, and fasting insulin levels in both South Asians and Europeans. Results are presented as percentage decrease in metabolic parameters for every 10% increase in physical activity levels (MET.minutes per week). A 10% increase in total physical activity was associated with 3.9% (95% CI: 3.6 – 4.3, P<0.001) decrease in HOMA-IR. Similarly, fasting glucose levels were lowered by 0.8% (95% CI: 0.7 – 0.9, P<0.001) while fasting insulin levels were reduced by 3.2% (95% CI: 2.8 – 3.5, P<0.001) with every 10 % increase in total physical activity per week. An increase in moderate to vigorous physical activity levels was also associated with similar reductions in HOMA-IR, fasting glucose and fasting insulin levels (all P <0.001). The effect size for relationship between physical activity levels and metabolic parameters was higher in Europeans compared to South Asians for the same level of physical activity (P_{het} <0.01, **table 5.10**). Association between physical activity levels and metabolic parameters was independent of adiposity (**table 5.11**).

Levels of HOMA-IR, fasting glucose and fasting insulin were highest amongst the participants in 1st quartile of total physical activity per week. Metabolic parameter levels decreased with higher physical activity quartiles and were lowest amongst participants in the 4th quartile of total physical activity. However, for each quartile of total physical activity per week the levels of HOMA-IR, fasting glucose and fasting insulin were significantly higher in South Asians compared to Europeans (P<0.001) (**figure 5.9**).

Table 5.10 Relationship of physical activity (MET.minutes/week) with fasting glucose levels, fasting insulin levels and HOMA-IR. Results are presented as % decrease (95%CI) in the respective metabolic parameter per 10% increase in physical activity (MET.minutes/week). P_{het} is for comparison of results between Europeans and South Asians.

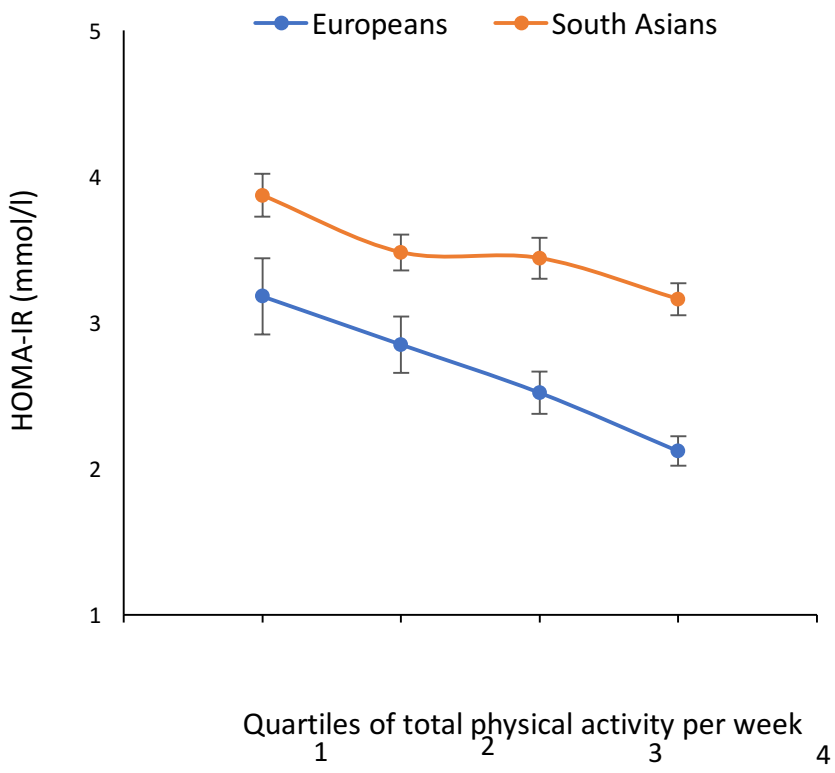
	All participants		Europeans		South Asians		
	% decrease (95%CI)	P	% decrease (95%CI)	P	% decrease (95%CI)	P	Phet
HOMA-IR							
Total physical activity	3.9 (3.6 – 4.3)	$9.8x10^{-101}$	4.3 (3.8 – 4.9)	$6.2x10^{-55}$	3.6 (3.2 – 4.0)	$9.9x10^{-50}$	0.002
Moderate to vigorous physical activity	1.2 (1.1 – 1.3)	$1.9x10^{-62}$	1.5 (1.3 – 1.7)	$2.5x10^{-47}$	1.0 (0.7 – 1.1)	$3.2x10^{-22}$	$7x10^{-07}$
Glucose							
Total physical activity	0.8 (0.7 – 0.9)	<0.0001	0.8 (0.7 - 0.9)	$1.5x^{-106}$	0.9 (0.8 – 0.9)	$1.3x10^{-220}$	0.005
Moderate to vigorous physical activity	0.1 (0.09 – 0.12)	$1.1x10^{-46}$	0.1 (0.08 – 0.13)	$3.0x10^{-18}$	0.1 (0.09 – 0.13)	$3.6x10^{-30}$	0.6
Insulin							
Total physical activity	3.2 (2.8 – 3.5)	$7.6x10^{-67}$	3.6 (3.0 – 4.1)	$1.5x10^{-41}$	2.7 (2.3 – 3.1)	$7.0x10^{-30}$	0.0003
Moderate to vigorous physical activity	1.1 (1.0 – 1.2)	$3.4x10^{-56}$	1.4 (1.2 – 1.6)	$3.5x10^{-45}$	0.8 (0.7 - 0.9)	$1.0x10^{-18}$	$2x10^{-07}$

Table 5.11 Relationship of physical activity (MET.minutes) with fasting glucose levels, fasting insulin levels and HOMA-IR after adjusting for adiposity (BMI and WHR). Results are presented as % decrease (95%CI) in the respective metabolic parameter per 10% percent change in physical activity (MET.minutes).

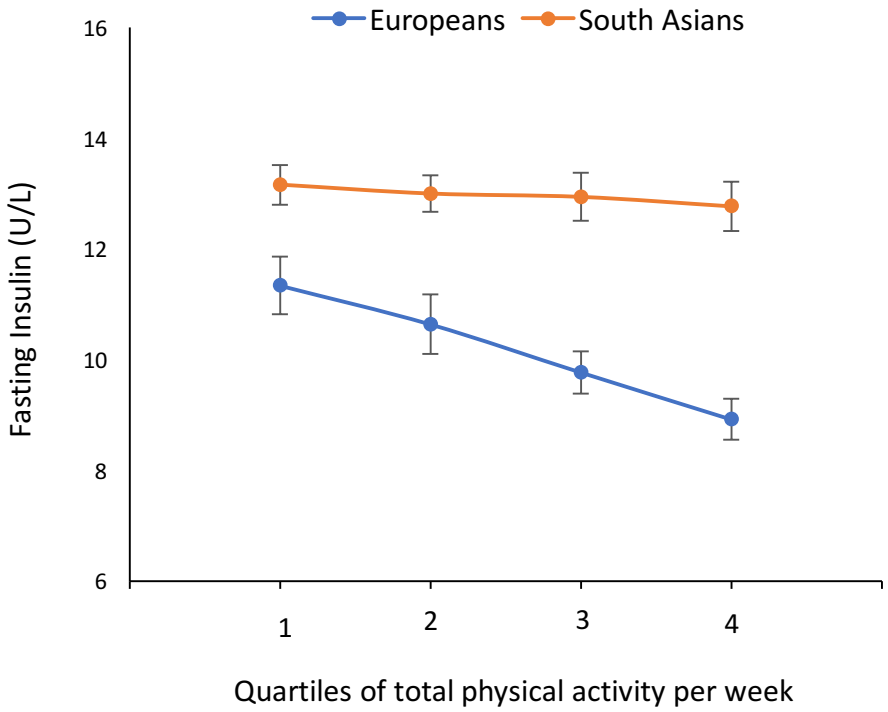
	HOMA-IR		GLUCOSE		INSULIN	
	% decrease (95% CI)	P	% decrease (95% CI)	P	% decrease (95% CI)	P
MET.minutes per week						
Total physical activity	1.1 (0.8-1.4)	$1x10^{-86}$	0.7(0.6-0.8)	$3x10^{-232}$	0.4 (0.1-0.6)	$5.2x10^{-56}$
Moderate to vigorous physical activity	0.5 (0.4-0.6)	$5x10^{-56}$	0.1 (0.06-0.12)	$3.3x10^{-32}$	0.5 (0.4-0.6)	$1.6x10^{-50}$

Figure 5.9 Levels of HOMA-IR, glucose and insulin amongst South Asians and Europeans. Results are presented as mean (95% CI) for quartiles of physical activity levels per week. Independent samples student's t-test was used to compare the mean levels of metabolic parameters between South Asians and Europeans across all quartiles of physical activity; P<0.001 at each category.

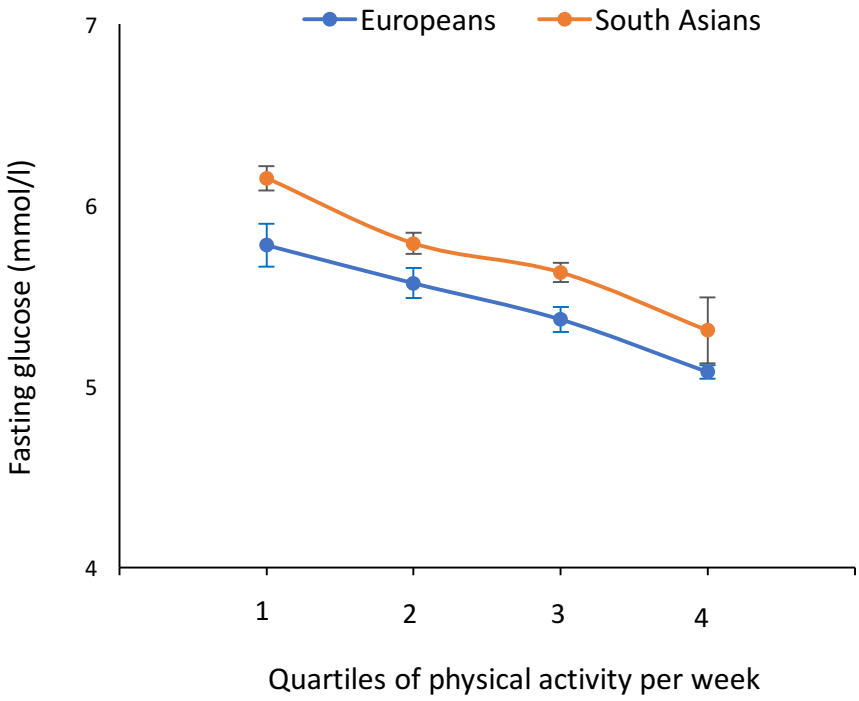
HOMA-IR



Fasting insulin



Fasting glucose



5.6.8. Contribution of physical activity to difference in risk of new-onset T2D and metabolic disturbances between South Asians and Europeans

I used logistic regression to quantify the contribution of physical activity to the higher risk of new-onset T2D in South Asians compared to Europeans (**table 5.12**) The age, sex and adiposity adjusted relative risk of T2D was 2.8 (95% CI: 2.5-3.2, $P=6.3 \times 10^{-58}$) in South Asians compared to Europeans. After adjusting for total physical activity levels, the relative risk of T2D in South Asians, compared to Europeans, was reduced to 2.3 (95% CI: 2.0-2.7, $P=4.5 \times 10^{-35}$). Similar results were obtained for moderate to vigorous physical activity levels (**table 5.12**).

I used multiple linear regression to quantify the contribution of physical activity to higher metabolic disturbances amongst South Asians compared to Europeans (**table 5.13**). Results are expressed as percentage difference in respective metabolic parameters amongst South Asians and Europeans, after adjustment for potential confounders (age and sex). I show that HOMA-IR levels are 16% (95% CI: 15.5 -17.5, P<0.001) higher amongst South Asians than Europeans. After adjusting for total physical activity, the difference in HOMA-IR between South Asians and Europeans was reduced to 12% (95% CI:10.9 – 13.2, P<0.001).

Table 5.12 Contribution of physical activity towards the higher burden of T2D amongst South Asians compared to Europeans. Beta coefficient from logistic regression represents the relative risk of T2D in South Asians compared to Europeans.

Adjusted for:	**South Asians vs Europeans**	
	RR (95% CI)	**P**
Age/sex	3.3 (2.9 - 3.7)	2.3×10^{-67}
Age/sex + BMI	3.3 (2.9 - 3.7)	9.5×10^{-38}
Age/sex + WHR	2.8 (2.5 - 3.2)	6.3×10^{-58}
Age/sex + BMI + WHR	3.3 (2.9 - 3.8)	1.1×10^{-75}
Age/sex + BMI + WHR + total physical activity	2.3 (2.0 – 2.7)	4.5×10^{-35}
Age, sex, BMI, WHR, moderate to vigorous physical activity.	2.8 (2.5 – 3.3)	2.0×10^{-53}

Table 5.13 Contribution of physical activity towards the excess levels of metabolic disturbances amongst South Asians compared to Europeans. Beta coefficient from multiple linear regression represents the percentage difference in metabolic parameters between South Asians and Europeans before and after adjustment for physical activity (MET.minutes) per week.

	HOMA-IR		GLUCOSE		INSULIN	
	% diff (95% CI)	**P**	**% diff (95% CI)**	**P**	**% diff (95% CI)**	**P**
Unadjusted for physical activity	16.5 (15.5 – 17.5)	6.4×10^{-176}	3.0 (2.7 - 3.3)	9.2×10^{-14}	13.5 (12.7 – 14.4)	9.1×10^{-182}
Adjusted for MET.minutes per week in:						
Total physical activity	12.1 (10.9 - 13.2)	7.8×10^{-36}	1.6 (1.3 – 1.9)	2.4×10^{-44}	10.5 (09.5 - 11.5)	2.2×10^{-50}
Moderate to vigorous physical activity	15.3 (14.3 - 16.3)	5.8×10^{-93}	2.5 (2.3 – 3.7)	6.0×10^{-117}	12.1 (11.2 - 13.0)	8.3×10^{-100}

Compared to Europeans South Asians showed 3% (95% CI: 2.7 – 3.3, P<0.001) higher fasting glucose concentrations. Percentage difference in fasting glucose levels, between South Asians and Europeans, decreased to 1.6% (95% CI: 1.3 – 1.9, P<0.001) after adjusting for total physical activity per week. In addition, difference in fasting insulin levels was lowered from 13% to 10% (95% CI: 12.7 – 14.4 and 9.5 – 11.5 respectively, both P<0.001) after adjusting for total physical activity levels. Similar results were found when adjusting for moderate to vigorous physical activity levels. However, physical activity did not completely account for differences in HOMA-IR or fasting glucose and insulin levels between South Asians and Europeans (**table 5.13**).

5.6.9. Population risk of T2D attributable to physical inactivity in South Asians and Europeans

Prevalence of physical inactivity and relative risks (RRs) of T2D varied across the different cut-off categories of physical inactivity (**table 5.14**). Physical inactivity was considered as a binary variable and was defined as physical activity levels less than the given threshold level; 600 MET.minutes per week was the primary threshold to define physical inactivity, based on national recommendations, but as sensitivity analyses I used a range of alternate thresholds (450, 750 and 1000 MET.minutes per week). Proportion of South Asians and Europeans failing to achieve at least 600 MET.minutes per week was 40.6% and 52.2% respectively. The relative risk of T2D amongst participants with less than 600 MET.minutes per week was 2.42 in Europeans and 1.35 in South Asians (both P<0.001).

The population risk of T2D attributable to physical inactivity in both South Asians and Europeans is summarised in **table 5.14**. The T2D population attributable risk (%) for achieving less than 600 MET.minutes per week was ~37% in Europeans and ~16% in South Asians. As the threshold for defining physical inactivity was increased from achieving a minimum of 450 MET.minutes per week to achieving at least 1000 MET.minutes per week, the proportion of physically inactive Europeans and South Asians increased, and so did the associated T2D population attributable risk for physical inactivity. Results for alternative definitions of physical inactivity are shown, as sensitivity analyses in **table 5.14**.

Table 5.14 T2D attributable to physical inactivity in Europeans and South Asians.

Risk Factor	Proportion of population exposed (%)		Relative risk of T2D		Population Attributable Risk (%)	
Physical inactivity levels	**Europeans**	**South Asians**	**Europeans**	**South Asians**	**Europeans**	**South Asians**
Less than 450 MET.minutes per week	33.0	44.3	2.42	1.32	32.0	12.6
Less than 600 MET.minutes per week	40.6	52.2	2.42	1.35	36.6	15.6
Less than 750 MET.minutes per week	47.2	58.4	2.37	1.42	39.2	19.9
Less than 1000 MET.minutes per week	54.7	65.8	2.60	1.54	46.7	26.1

5.7. Discussion

This study reaffirms the important association between low levels of physical activity and incident T2D, in both South Asians and Europeans. For the first time, physical activity has been objectively quantified amongst South Asians, and I demonstrate that measured physical activity is associated with reduced risk of incident T2D in both ethnic groups, though the magnitude of effect was higher in Europeans than South Asians.

In keeping with previous prospective data, a physically active lifestyle is associated with lower incidence of T2D. An 8 years follow-up study comprising female registered nurses, aged 34–59 years demonstrated that nurses who engaged in moderate to vigorous physical activity at least once a week had a lower incidence of self-reported T2D than those who did not engage in weekly exercise[276]. Similar findings were highlighted in a 5-year prospective study of male physicians aged 40–84 years, which showed lower rates of T2D in the most physically active[271].

My study supports the view that physical activity reduces the risk of T2D through improvements in insulin sensitivity[179] and glucose metabolism. There was a significant reduction in both insulin resistance and fasting glucose and insulin levels with increased physical activity levels amongst South Asians and Europeans, although the difference in HOMA-IR, glucose levels and insulin levels between South Asians and Europeans, was not accounted by the low physical activity levels amongst South Asians. Present study mirrors the findings of other large prospective studies which demonstrated that the relation between physical activity and T2D development persists when body mass index is added to the model[271,277-279]. The Da Qing

intervention Study[172] has demonstrated the beneficial role of physical activity in reducing the incidence of T2D independent of adiposity. The study reported a 46% reduction in T2D incidence, in the exercise intervention group, without a significant change in body mass index and this beneficial effect of physical activity was evident in both lean (body mass index, <25 kg/m2) and overweight (body mass index, ≥25 kg/m2) participants. My results also show the beneficial effects of physical activity in reducing risk of hyperglycaemia, insulin resistance and T2D are independent of adiposity.

Results of my study support the view that beneficial effects of physical activity are derived through mechanisms influencing glucose metabolism. Physical activity has been proven to improve glycaemic control by reinforcing insulin action and promoting glucose absorption into muscle, independent of insulin action[280-282.] The incidence of T2D rises with increasing blood glucose levels, even at levels below the threshold for IGR[283]. Thus, a reduction in blood glucose levels, because of increased physical activity, may reduce the excess risk of T2D in South Asians. In the Finnish Diabetes Prevention Study, a reduction of 0.9 mmol/l in the blood glucose levels was associated with a risk reduction of 58% in the incidence of T2D[171,284]. My results are in line with the lifestyle intervention studies that document reductions in incidence of T2D in patients with IGR. My study shows that difference in T2D risk amongst South Asians and Europeans can be reduced through increase in levels of physical activity. Achieving at least 600 MET.minutes per week may remove 16% of the T2D burden in South Asians. This is an important public health message, which has the potential to reduce development and progression of T2D in this high-risk population group.

Physical activity levels are associated with lower insulin resistance in both South Asians and Europeans. Importantly, these improvements in insulin levels and insulin resistance were independent of adiposity which is known to influence risk of T2D development. These results suggest that daily physical activity levels are an important determinant of T2D risk and associated metabolic disturbances in South Asians. Large observational trials confirm the association between physical activity and insulin resistance[181]. A single session of moderate to vigorous physical activity (exercise) may lead to an improvement in insulin resistance and this beneficial effect may last for several hours or even days[285,286]. Therefore, an increase in daily physical activity, even if it does not reach the recommended guidelines or does not cause sufficient weight loss, may provide a cost-effective option to reduce high insulin resistance and T2D risk in South Asians and Europeans both.

Compared to Europeans, South Asians had higher risk of new-onset T2D and associated metabolic disturbances, for similar levels of physical activity. These results indicate that South Asians may have to engage in greater levels of physical activity than Europeans to exhibit a similar risk profile for T2D. Current physical activity guidelines recommend at least 150 minutes of moderate to vigorous physical activity per week, for all populations[287-289]. These physical activity recommendations are based on data from European populations. My findings have potential implications for physical activity guidance to take ethnicity into account. In addition, my results also support previous evidence of reduced fat oxidation during exercise in South Asians compared to Europeans, and this is likely to contribute to their adverse risk profile for T2D. Moreover, cardiorespiratory fitness has been shown to have a strong heritable component[290,291], it is likely that there may be a genetic component associated with

the reduced effect of physical activity levels in South Asians. My results are in line with a recent study demonstrating that the relationship of physical activity with metabolic risk factors was significantly different in South Asians than in Europeans. But these findings were limited to a relatively small cohort of middle aged men, and cross-sectional study design[260]. Further research should be conducted to evaluate the possible environmental and genetic factors predicting the relationship between physical activity and metabolic health in South Asian population.

The main strengths of my study include the use of an objective and validated measure of physical activity in a representative UK South Asian cohort. The accelerometer used for imputation of objective physical activity was first validated in this population (**chapter 3**). Previous cross sectional studies have used accelerometer in a non-representative South Asian population without prior validation. The contribution of physical activity levels to the excess risk of new-onset T2D in South Asians compared to Europeans has not been investigated before. However, this study has several limitations. Although quantitative measures of physical activity are more robust than questionnaire based tools of self-reported physical activity, they are not practical in the setting of a large population based study. Therefore, I had to rely on imputed accelerometer data collected in a subset of this population, which may not necessarily reflect actual physical activity carried out by individual participants. Although my analyses accounted for the confounding effects of age, sex, and adiposity, the influence of important lifestyle factors such as diet were not assessed. Individuals who engage in higher physical activity levels are more likely to follow healthier diets than those who perform low intensity physical activity. In addition, the

HOMA model is not the most robust measure of insulin resistance, and more sensitive techniques exist, but again are not practical for use on a large scale.

In conclusion, I show that the incidence of T2D and related glycaemic disturbances are ~3 fold higher amongst South Asians compared to Europeans. Low levels of physical activity are an independent risk factor in South Asians that may account for an important proportion of their increased T2D risk compared to Europeans. My study shows that through efforts to increase levels of physical activity, it is possible to reduce, but not eliminate, the higher burden of T2D, insulin resistance and related complications amongst South Asians compared to Europeans. An international programme to identify environmental and genetic susceptibility factors underlying the increased risk of T2D and related glycaemic disturbances amongst South Asians is needed.

Chapter 6: Discussion

This is the first study to determine accuracy of accelerometers amongst South Asians, quantify physical activity by using accelerometers in a representative South Asian population and determine the association of physical activity to the increased risk of T2D in UK South Asians compared to Europeans.

6.1. Clinical characteristics

Recent data suggest that the prevalence of T2D is 2-3 times higher in South Asians compared to Europeans. Holman et al[292] compared the prevalence of T2D between South Asians and Europeans living in England in 2010. Results from this study estimated that the prevalence of T2D was ~2 times higher in South Asians compared to Europeans (14.0% vs. 6.9% respectively). A meta-analysis of international epidemiological studies and health examination surveys, by Danaei et al[21], found large increases in T2D prevalence and fasting plasma glucose levels amongst South Asian males. In the UK, Bhopal *et al*[293] conducted an analysis of the Health Survey for England (1999–2004) and reported a significant increase in T2D prevalence amongst South Asians. My findings are in line with the previous studies showing that T2D prevalence is higher in UK South Asians compared to Europeans (11.9% vs 4.3% respectively). The incidence of T2D, over mean 9 years of follow-up, was also ~3 times higher in UK South Asians than Europeans in the LOLIPOP cohort. In addition, family history of T2D was more common amongst South Asians compared to Europeans ($P<0.001$). My results support the view that there is an increased propensity for South Asians to develop T2D compared to Europeans.

My results support the evidence that South Asians have higher levels of metabolic disturbances compared to Europeans. South Asians had higher fasting

glucose, HbA1c, HOMA IR and triglycerides levels, and lower HDL cholesterol compared to Europeans. On the other hand, the conventional cardiac risk factors of high blood pressure and smoking were lower in South Asians than in Europeans. This pattern of IGR and insulin resistance, associated with high fasting glucose and insulin levels, reduced HDL cholesterol concentration and increased plasma triglyceride levels, has been consistently reported amongst South Asians[13,294,295]. In a multi-ethnic study conducted in Canada[296], participants with South Asian origin had an increased prevalence of T2D and IGT, reduced HDL cholesterol and raised triglyceride levels compared to participants with European origin.

In my study the waist hip ratio was higher amongst UK South Asians compared to Europeans at similar levels of BMI. This is consistent with the previous studies that report South Asians exhibit greater tendencies toward visceral fat deposition and central obesity than Europeans. Recent investigations have revealed that South Asians are likely to have more central obesity for any degree of BMI compared with European populations[93,130,297,298]. Higher levels of central obesity is accompanied with a higher degree of insulin resistance amongst South Asians compared to Europeans for the same BMI[93,299]. Because of these observations, the WHO has recommended lower BMI cut-off points for overweight (23 kg/m2) and obesity (25 kg/m2) in South Asians[300]. Accordingly, the cut-off for abnormal waist circumference has also been lowered to 80 cm and 90 cm in South Asian women and men respectively. The IDF has also recommended lower waist circumference cut-offs in South Asians in its guidelines for metabolic syndrome classification[301].

South Asians who developed T2D during follow-up had higher body mass index, waist circumference and waist-hip ratio, and higher fasting glucose, insulin, HOMA-IR and HbA1c compared to controls. These results are in agreement with the findings from the SABRE study[7]. The SABRE study has reported that at baseline (1988-1991) the UK South Asian participants had higher prevalence of insulin resistance, cardiometabolic risk factors and a higher prevalence of central obesity. My results suggest the role of the above mentioned metabolic factors in the development of T2D amongst South Asians. However, these factors do not explain the excess risk of T2D amongst South Asians compared to Europeans.

6.2. Accuracy of accelerometers

I have evaluated the accuracy of three commercially available physical activity accelerometers: (i) Actigraph GT3X+, (ii) Geneactiv and (iii) Actiheart, among South Asians and Europeans. Actiheart includes heart rate monitoring in addition to accelerometry and incorporates this information into estimation of physical activity energy expenditure. Physical activity energy expenditure was measured by wearing the accelerometers on four different positions: (i) waist, (ii) wrist, (iii) ankle and (iv) chest. My aim was to: (i) identify the accelerometer, and accelerometer position, that most accurately quantifies physical activity amongst South Asians, and (ii). compare the accuracy of the accelerometers between South Asians and Europeans.

All the accelerometers used in my study have been calibrated previously against Doubly labelled water, calorimeter and treadmill tests in Europeans and have shown good accuracy and reproducibility[205,208,210,216,218]. Published studies show that the relationship between energy expenditure measured by the accelerometers and the

standard/criterion varies with both technical factors[219,223,302] (like device positioning, epoch length) as well as biological factors[250] (like BMI, WHR, waist circumference). These observations raise the possibility that the accuracy of accelerometers may vary between South Asians and Europeans because of the known anthropometric and metabolic differences between the two populations. My analyses suggest that the devices measure energy expenditure equally well in the two populations. Although all the three devices evaluated consistently underestimate actual energy expenditure, device performance is similar between South Asians and Europeans. Differences in anthropometric measures do not influence the measurements from Actigraph GT3X+ and Geneactiv. However, for the Actiheart device, lower levels of adiposity were associated with a greater degree of error.

I show that the Actigraph GT3X+ worn on the ankle or waist measures energy expenditure during a treadmill test more accurately than both the Geneactiv device in similar positions, and the chest-worn Actiheart device. My results support the view that Actigraph GT3X+ is the most accurate accelerometery device for measuring physical activity in population studies. This is consistent with previous studies which support the validity of the Actigraph device under both laboratory [219] as well as free-living conditions [210,216]. In addition, when compared to other physical activity sensors Actigraph GT3X+ has shown better performance.

Studies have compared the efficacy of wrist worn accelerometers with waist worn accelerometers while participants walk on a treadmill[256]. These studies report that wrist worn accelerometers are less accurate compared to waist worn accelerometers. Moreover, these results reflect the relative lack of contribution of hand

movement to physical activity during walking. Similarly, my results show that in contrast to accelerometers worn on other body positions, wrist-worn accelerometers showed poor association with the actual energy expenditure and captured minimal energy expenditure among both South Asians and Europeans.

In summary, I show that the Actigraph GT3X+ is more accurate than the Geneactiv and Actiheart devices for measurement of physical activity during walking, and that energy expenditure during walking is best measured by devices worn on the ankle and waist. The performance of the Actigraph GT3X+ is similar in South Asians and Europeans, and does not appear to be materially influenced by anthropometric parameters. My results support the view that the Actigraph GT3X+ is a suitable device for measurement of energy expenditure during physical activity in trans-ethnic epidemiological studies.

My results suggest that the Actigraph GT3X+ worn on the ankle or waist is a suitable device for objective measurement of energy expenditure during physical activity amongst South Asians, and for comparison of energy expenditure between South Asian and European populations. On the other hand, Actiheart may be less suitable for use in studies of energy expenditure from physical activity in population studies.

6.3. Physical activity levels

The results presented in the current study confirmed that South Asians had lower levels of moderate, vigorous and total physical activity compared to Europeans ($P<0.001$), measured objectively using accelerometers. Total energy expenditure per

week calculated by the Actigraph GT3X+ was ~31% lower amongst South Asians than Europeans. Low levels of energy expenditure amongst South Asians were independent of differences in age, sex or adiposity, compared to Europeans. These results support previous studies that report ~50 - 70% lower levels of leisure time and total physical activity amongst South Asians than Europeans. More recent data, however, has reported a smaller difference indicating that there may be a positive change in attitude towards physical activity in South Asian men and women, however their physical activity levels remain lower than Europeans.

Almost all previously published studies used physical activity questionnaires to measure and compare physical activity levels amongst South Asians and Europeans. The limitations of these self-report measures, such as recall bias, over reporting of moderate to vigorous physical activity and misinterpretation of questions, are well recognized. Hunt et al[303] has recently mentioned problems which can arise when questionnaires designed by and for native English speakers are translated into other languages. Moreover, these self-report measures have been validated in Europeans but not in South Asians. A recent study[260] reported low levels of objectively measured physical activity amongst UK South Asians compared to Europeans without prior validation of the devices amongst South Asians. Moreover, this study was carried out in a population sample with low response rate (<5%) and exclusively male, and therefore unrepresentative of the UK South Asian population. My results extend current knowledge by providing quantitative assessment of physical activity, after validation of the accelerometers (chapter 3), in a representative sample of South Asian men and women (response rate 65%).

There is not much literature available on the reasons underlying low levels of physical activity amongst South Asians but may include a lack of understanding regarding the health benefits associated with regular physical activity, as well as cultural expectations and barriers to participation in recreational activities[304]. Other factors suggested to be associated with physical inactivity amongst South Asians include skilled workers and professionals, higher education, cost and female sex[305-308]. In addition, leisure time and transport related physical activity has been reported to be much lower amongst South Asians compared to other activity domains. Hence, it is crucial to understand the social, economic, and cultural factors associated with low physical activity levels amongst South Asians in order to deliver effective physical activity interventions in this population.

Lower levels of physical activity have been associated with higher levels of adiposity, insulin resistance and associated metabolic disturbances[309-311]. The lower levels of physical activity among South Asians may contribute towards the higher burden of T2D amongst South Asians; dependent and/or independent of its effects on adiposity and insulin resistance and associated metabolic disturbances. These findings favour interventions that emphasize increased levels of physical activity in daily routines. These interventions, however need to take account of social, cultural and religious factors that may determine the physical activity levels amongst South Asians.

6.4. Cross sectional study

I have presented the cross-sectional associations of objectively measured physical activity with insulin resistance and related metabolic risk factors amongst UK

South Asians and Europeans. My results show that physical activity energy expenditure, measured using Actigraph GT3X+, is independently and inversely associated with glucose, HbA1c, and insulin resistance. The direction of association was similar in the two populations. Moreover, the relationship of physical activity with metabolic parameters was independent of differences in age, sex or adiposity.

My results are comparable with published data which show that increased physical activity is associated with a reduction in glucose and HbA1c concentrations in European populations[262,263,312]. Fasting glucose levels were higher in South Asians than in Europeans. Difference in fasting glucose levels between the two populations was no longer significant after adjusting for total physical activity levels. My findings indicate that lower levels of physical activity amongst South Asians may account for their higher concentrations of glucose compared to Europeans. Abnormal glucose metabolism underlies impaired glucose tolerance and T2D. Low physical activity amongst South Asians may therefore have a role in the increased risk of impaired glucose tolerance and T2D in this population, through an effect on glucose metabolism. My findings are consistent with experimental studies which show that physical activity stimulates translocation of GLUT4 glucose transporters, the rate-limiting step in glucose metabolism, in skeletal muscle[313]. These results suggest that South Asians should engage in greater levels of physical activity to minimise their metabolic risk.

Previous studies carried out in Europeans have reported a strong association of total physical activity levels with insulin resistance[179]. My results report that an increase in physical activity levels is associated with reduced insulin resistance

amongst both South Asians and Europeans. This improvement in insulin resistance as a result of increased total physical activity may occur with and/or without physical activity related weight loss[314]. The independent effect of physical activity on insulin resistance suggests that an increase in daily total physical activity has a beneficial role in reducing the risk of metabolic disorders and T2D.

My findings suggest that higher concentrations of glucose amongst South Asians are in part accounted for by their lower levels of physical activity compared to Europeans. Abnormal glucose metabolism underlies T2D and impaired glucose tolerance, both associated with major microvascular and macrovascular complications including cardiovascular disease. Prospective studies show that elevated glucose despite being in the normal range is a risk factor for cardiovascular disease[315,316]. Low physical activity amongst South Asians may therefore have a role in the increased risk of cardiovascular disease risk in this population, through an effect on glucose metabolism. My results show that insulin resistance, as measured by HOMA-IR, and related metabolic disturbances are more common amongst South Asians than Europeans. However lower physical activity did not explain the higher burden of these metabolic abnormalities amongst South Asians.

6.5. Prospective study

Physical activity is recognized as an important determinant of T2D amongst Europeans. Prospective studies have documented lower incidence of T2D for daily physical activity levels[238,276]. In a post hoc analysis of the Finnish Diabetes Prevention Study, brisk walking for at least 2.5 hours a week was associated with a 63–69% lower incidence of T2D compared to those who walk for less than 1 hour[317]. Manson et al.[271]

carried out a large cohort study that examined the association between vigorous physical activity and incident T2D among 40 to 84 years old male physicians. Results of the study demonstrated an inverse association between the frequency of vigorous physical activity and T2D development. Another study by Hu et al.[276] investigated the association of moderate and vigorous physical activity with incident T2D among participants of the Nurses' Health Study. This study demonstrated that both moderate and vigorous intensity physical activity were associated with a reduced risk of incident T2D.

My results confirm a 3-fold higher risk of new-onset T2D in UK South Asians compared to Europeans. The high risk of new-onset T2D amongst South Asians compared to Europeans was however, not explained by the differences in age, sex, adiposity and physical activity levels. Moreover, the high burden of insulin resistance and T2D can be reduced significantly in South Asians after increasing daily physical activity levels. Reduction in risk of insulin resistance and T2D was relatively higher in Europeans compared to South Asians for similar levels of physical activity. These results indicate that South Asians may respond differently to physical activity. Recent data suggest that compared with Europeans, South Asians oxidise less fat during exercise[318] suggesting that South Asians may need to perform more physical activity to exhibit a metabolic risk profile similar to Europeans[319]. Current physical activity guidelines recommend at least 150 minutes of moderate to vigorous physical activity per week, for all populations[287-289]. These physical activity recommendations are based on data from European populations. My findings have potential implications for physical activity guidance to take ethnicity into account.

Results of my study support the view that beneficial effects of physical activity are derived through mechanisms influencing glucose metabolism. Physical activity has been proven to improve glycaemic control by reinforcing insulin action and promoting glucose absorption into muscle, independent of insulin action[280-282.] The incidence of T2D rises with increasing blood glucose levels, even at levels below the threshold for IGR[283]. Thus, a reduction in blood glucose levels, because of increased physical activity, may reduce the excess risk of T2D in South Asians. In the Finnish Diabetes Prevention Study, a reduction of 0.9 mmol/l in the blood glucose levels was associated with a risk reduction of 58% in the incidence of T2D[171,284]. My results are in line with the lifestyle intervention studies that document reductions in incidence of T2D in patients with IGR.

Physical activity levels were associated with lower insulin resistance in both South Asians and Europeans. Importantly, these improvements in insulin levels and insulin resistance were independent of adiposity which is known to influence risk of T2D development. Large observational trials confirm the association between physical activity and insulin resistance[181]. A single session of moderate to vigorous physical activity (exercise) may lead to an improvement in insulin resistance and this beneficial effect may last for several hours or even days[285,286]. Therefore, an increase in daily physical activity, even if it does not reach the recommended guidelines or does not cause sufficient weight loss, may provide a cost-effective option to reduce high insulin resistance and T2D risk in South Asians and Europeans both.

My results confirm a protective role for physical activity among men and women of both South Asian and European ancestry. The preventive effect of physical

activity on T2D even after adjustment for adiposity, suggests that the effect of physical activity on T2D is independent of adiposity. Data from interventional studies amongst South Asians and Europeans confirm an important contribution made by lifestyle interventions, including increased physical activity levels, in attenuating risk of future T2D[171,203]. Therefore, my findings do not refute the important association of physical activity and T2D risk among South Asians.

6.6. Contribution of physical activity to high T2D risk in South Asians

My data show that through intense efforts to increase levels of physical activity, it is possible to reduce the higher burden of T2D, insulin resistance and related glycaemic disturbances amongst South Asians and Europeans. Achieving at least 600 MET.minutes per week may remove 16% of the T2D burden in South Asians compared to 37% in Europeans. This is an important public health message, which has the potential to reduce development and progression of T2D in South Asians, a high-risk population group. However, the difference in the risk of T2D and related metabolic disturbances amongst South Asians and Europeans could not be explained by differences in physical activity levels between the two populations. An international programme to identify environmental and genetic susceptibility factors underlying the increased prevalence of T2D and related glycaemic disturbances amongst South Asians is needed.

Current estimates indicate that known T2D risk alleles account for ~10% of genetic heritability[113], suggesting further genetic influences remain to be discovered. Given the high rates of T2D amongst South Asians, unaccounted for by established environmental and genetic risk factors, it is likely that population-specific genetic

variants or undiscovered shared common genetic polymorphisms may explain their increased risk.

Recent data highlight the role of epigenetic modifications in the development of T2D. Epigenetic regulation refers to heritable changes in gene expression and phenotype that are not determined by changes in DNA sequence[320]. Birth cohort studies show that maternal undernutrition, low birth-weight, and rapid postnatal child growth are all associated with increased risk of T2D in the off-spring[321]. These risks appear to be mediated through epigenetic modification and may be trans-generational. More than 96% of low birth-weight occurs in the developing world, with highest incidence in South Asians (31% of live births)[322]. The Pune Maternal Nutrition Study, a prospective population-based observational study, was conducted on rural South Asian women and their offspring. Results from the study showed that South Asian mothers were, on average, shorter (mean 152cm) and thinner (mean BMI 18.1kg/m2) than their European counterparts and full-term South Asian neonates were ~700g lighter than the average European[321]. This low birth weight in neonates is accompanied by changes in body composition with greater reduction in lean, muscle tissue than truncal fat. Birth cohort studies in India have confirmed the association of maternal undernutrition, low-birth weight and thinness in infancy with development of IGR and T2D later in life[321]. Risk of IGR and T2D is reported to be highest amongst South Asians who have shorter mothers, parents with lower BMI, low birth weight, thinness in infancy and greater weight gain during childhood and adolescence, independent of their adult BMI[323]. These observations of adverse intrauterine and postnatal exposures in South Asians raise the possibility that epigenetic modification of gene expression may contribute to increased susceptibility to T2D. Future

experiments amongst South Asians are needed to investigate the contribution of epigenetic factors to T2D the increased risk of T2D in this population compared to Europeans.

Present data suggest that higher physical activity levels for South Asians may be needed to exhibit a metabolic profile similar to Europeans. Research studies have demonstrated a heritable component to cardiorespiratory fitness (VO2max)[290,291]; thus, it seems likely that there will be a genetic contribution to the lower physical activity levels in South Asians. In addition, South Asians have been reported to have a reduced ability to oxidise fat during exercise compared with Europeans[318], suggesting that there may be innate physiological differences between South Asians and Europeans that may contribute to the reduced beneficial effect of physical activity in South Asians. Similar results from previous study in South Asians and Europeans are limited to a relatively small cohort of non-diabetic middle-aged men, and cross-sectional study design[260,319]. Future epidemiological and interventional studies, comparing the relationship between objectively measured physical activity and risk of T2D and related complications in South Asians and Europeans are needed to identify appropriate levels of physical activity to minimise T2D risk in South Asians. Current physical activity guidelines are similar for all ethnic groups. My results suggest that physical activity guidelines should be revised taking ethnicity into account. My results are also in agreement with previous studies demonstrating that South Asians have a reduced ability to oxidise fat during physical activity, compared to Europeans, which is likely to contribute to their adverse metabolic risk profile.

I have assessed the contribution of physical activity levels to the increased risk of T2D amongst South Asians compared to Europeans. However, to fully evaluate the role of the environment to T2D risk other important factors need consideration. People are exposed to and interact with multiple environments: the physical environment (chemical exposures and daily light/dark cycles), the "built" environment, the food environment, psychosocial environment and socio-economic environment. In addition, pollution of air and water, as well as passive chemical exposures, which can disrupt endocrine function[324] also form a part of environmental exposures[325]. Recent data indicate that sleep disturbances may lead to energy imbalance and insulin dysfunction[326]. The contribution of these factors to T2D amongst South Asians merit further evaluation in the setting of large epidemiological study.

6.7. Strengths and limitations of the study

Strengths of my analyses include use of a large representative population sample including UK South Asians and Europeans men and women. Errors with estimation of physical activity using questionnaires, in epidemiological studies, are well recognised[327]. The key strength of this study is that physical activity was measured with the use of an objective measure (accelerometer) which is essential in quantifying the real relationship between physical activity and metabolic and T2D risk. The use of objective physical activity measures can refine understanding of the protective mechanisms of physical activity to South Asian health. Although these accelerometers have been validated in Europeans repeatedly, their validity in South Asians was not known. I determined and compared the accuracy of three widely available accelerometers in UK South Asians and Europeans for the first time. To my knowledge

this is the first population study to report the contribution of physical activity levels to the excess risk of new-onset T2D in South Asians compared to Europeans.

My study has some limitations as well. I compared the physical activity energy expenditure measured by accelerometers with actual energy expenditure estimated based on speed and incline of the exercise treadmill, rather than directly measured energy expenditure from double labeled water or calorimetry. However, published studies show that estimates of energy expenditure based on speed and incline correlate closely with direct measurements from doubly-labeled water and calorimeter. Secondly, I validated accelerometers amongst participants in a hospital setting and limited the assessment of physical activity to energy expenditure during walking.

I carried out a cross sectional study to quantify physical activity levels using physical activity accelerometers amongst South Asian and European men and women. This study may be susceptible to confounding effects ("reverse causation"). I determined insulin resistance using HOMA-IR, which, although closely correlated with the gold standard Hyperinsulinaemic euglycaemic clamp, remains a less accurate measure of insulin resistance. Finally, although accelerometers are an objective measure of physical activity and their use has been validated against the gold standard under close supervision, their accuracy in free living individuals is lower, and my estimates of physical activity may be imprecise. Although objective physical activity measures, used in the prospective study, are more valid compared to self-report measures of physical activity, the objective physical activity values were imputed using accelerometer data collected in a subset of this population. The use of imputed

accelerometer data might have underestimated the role of physical activity in reducing the risk of T2D in South Asians and Europeans. As with all cross-sectional data sets, LOLIPOP may be subject to survival bias leading to under-representation of individuals with the most aggressive forms of T2D in the population sample. I did not examine the contribution of environmental factors known to limit physical activity, including neighbourhood safety, crowding, and access to exercise facilities; all the aforementioned factors may have confounded my association testing[328]. Although I considered potential confounding by age, sex, ethnicity and adiposity, yet the influence of other confounding variables such as diet was not assessed. Individuals who engage in higher physical activity levels are more likely to have healthy diets compared to those who perform lower levels of physical activity.

6.8. Conclusions

In conclusion, I show that physical activity measuring accelerometers are as effective in South Asians as they are in Europeans and Actigraph GT3X+ is the most accurate device for measuring physical activity levels amongst both South Asians and Europeans, across all the different body positions. I confirm a 3-fold higher risk of insulin resistance and T2D amongst South Asians compared to Europeans, unexplained by differences in age, sex, adiposity and physical activity levels. Accelerometery determined physical activity levels are ~31% lower amongst South Asians compared to Europeans. My results suggest the potential for increased physical activity to improve glucose metabolism and insulin resistance, that predict T2D risk, amongst South Asians, and help reduce their excess risk of T2D and its related complications. Furthermore, I show that an increase in physical activity levels

alone is unlikely to bridge the 3-fold excess risk of T2D in South Asians compared to Europeans.

South Asians make up the largest ethnic minority group in the UK. Given the higher risk of T2D in South Asian people compared with other groups, and the increased risk of complications, comprehensive management of risk factors in this group is essential. South Asians are a heterogeneous population, stratified by differences in religion, language, social and cultural practice. Therefore, specific and culturally appropriate advice on exercise (i.e. how much to do and examples of types of exercise) should be provided to help more people make lifestyle changes. Importantly, reduced physical activity is also seen in South Asian children, who are 13-times more likely to develop type 2 diabetes than white European children[329]. This highlights the need of educating the South Asians about the importance of physical activity at an early age, to help improve outcomes for this population.

LOLIPOP study forms the largest collection of South Asian men and women within a research effort world-wide, however, these results should be generalized to other South Asian groups with caution. Future work should include assessment of device performance under a wider range of activities in free-living conditions. To understand the potential contribution of physical activity to the prevention of type 2 diabetes amongst South Asians, future research should focus on the underlying mechanisms by which physical activity reduces the risk of T2D amongst South Asians and the associated genetic and environmental factors that may influence the effects of physical activity in South Asians.

6.9. Expected value of results

My findings support the fact that although genetic factors are important, the increased incidence of T2D and associated metabolic disturbances is strongly associated with low physical activity levels in South Asians. The DPP and IDDP study have provided evidence that lifestyle intervention before the development of diabetes in high risk groups may prevent or delay the onset of T2D. In the face of a rapid rise in T2D prevalence among South Asians, effective programmes need to be established, tailored for each population group, and rigorously evaluated, to reduce their risk of developing the condition.

The cornerstone of any intervention should be improved education of the community in a healthy lifestyle, increased physical activity, and thereby prevention of T2D, insulin resistance and associated metabolic disorders. Knowledge of the risks of low physical activity is poor among South Asian communities. Likewise, barriers to engaging in physical activity, such as women's roles in caring for family, physical modesty, safety and unmet information needs, have also been identified. In addition, lack of motivation, fear of symptoms during exercise and lack of time and money are also recognized barriers to engaging in physical activity. South Asian's access to health promotion is also hindered by language, and the failure of health providers to offer practical advice on diet, physical activity and reducing the risk of disease.

It is important to understand the different ways in which South Asians are physically active, so physical activity interventions can be tailored appropriately. Moreover, since the pattern of physical activity changes with age, age-appropriate interventions are necessary for all South Asian groups. Understanding the role of

individual socioeconomic class in physical activity patterns is important. Socioeconomic status may impact on physical activity patterns depending on the occupation, income, education levels and local facilities and resources.

Culturally appropriate interventions are required that involve a whole community. An example of one such intervention is the **ihealth-T2D study (H2020, P52272).** The study focuses on South Asian men and women living in India, Sri Lanka, Pakistan, and the United Kingdom. Study participants are from major cultural subgroups and from diverse social and economic backgrounds. South Asians at risk of T2D are identified using waist circumference and HbA1c. Participants are randomly allocated to intervention (where participants receive personalised diet plans and physical activity targets) and control arm. iHealth-T2D focuses on family-based approach and encourages all participants to involve their family members in the clinic sessions and in physical activities. However, far more research is required to provide an evidence base for health promotion in South Asians, with rigorous evaluation of culturally tailored community initiatives.

South Asians seem to be more insulin resistant, even at an early age. Great concern is caused by the lower physical activity levels and increasing levels of obesity and related insulin resistance among south Asian children. Physical activity programmes targeting school children should be developed to reduce childhood obesity an established risk factor for developing T2D later in life.

Collaboration between health, education, information, and agriculture ministries is essential to create awareness and to facilitate a healthy lifestyle among the population.

Creating awareness of the impact of low physical activity levels and educating people that increased physical activity is the best way of preventing and controlling T2D, through newspapers, national TV channels and radio channels, may help to promote healthy lifestyle and thus reduce the risk of T2D. Encouraging physical activity by the creation of amenities such as public spaces (e.g. parks) for walking or cycling is needed to facilitate healthy living. It is important to develop strategies to educate and motivate the public regarding the prevention of diabetes and associated complications. Public and private-sector organizations across all South Asian countries should work together, to measure the magnitude of the problem and design an integrated approach for preventing T2D.

In summary, my findings may be helpful in proposing guidelines or using physical activity in the prevention and control of T2D, major global health problem. Such preventative efforts need to be directed both at individual and population levels. Moreover, these lifestyle changes should be culturally sensitive and aggressive, and should start early to reduce the risk of T2D in South Asians, a highly susceptible population.

Recommendation for future research

I have described in my thesis the effectiveness of physical activity monitors in measuring physical activity in South Asians and described the beneficial role of daily physical activity levels in reducing the high burden of T2D in South Asians. More physical activity interventions targeting South Asian populations should be conducted which should report:

1. How interventions are culturally adapted

2. Types of behaviour change methods and theories that are used to reinforce interventions
3. Metabolic health outcomes by measures of socioeconomic status
4. Execution and maintenance costs of the interventions.

Development of effective physical activity interventions may require both qualitative and quantitative research on knowledge, attitudes, behaviours, and insights. Additional research is required into the differential effects of physical activity interventions for South Asians compared with other ethnic populations. So far existing universal interventions are adapted in any population. However, there may be a need to develop new population specific interventions.

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