

Physical activity status, chronic stress, cardiovascular risk factors and telomere length in an urban South African teachers' cohort: The SABPA study

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Toe ek gedink het my voete gly, het u troue liefde my regop gehou, Here. Toe ek met baie onrus in my binneste sit, het u vertroosting my tot rus gebring.

~ Psalm 94:18&19 ~

DECLARATION

This thesis is submitted in article format and includes three research articles, chapters 3, 4 and 5. The promoters, Prof Hans de Ridder, Prof Leoné Malan and Dr Mariëtte Swanepoel, hereby give permission to the principal author, Ms Erna Bruwer, to include these research articles as part of her doctoral thesis and submit this document for examination purposes. The contributions (advisory and supportive) of the promoters and co-authors to the articles were kept within reasonable limits. This thesis then serves as fulfilment of the Ph.D. requirements within the Physical Activity, Sport and Recreation research focus area (PHASRec) in the Faculty of Health Sciences (NWU, Potchefstroom Campus).

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SUMMARY

The dose-response relationship between physical activity (PA), disease and mortality has primarily been obtained from self-report questionnaires in Western populations. A major limitation of self-reported PA is the likelihood of measurement error and these recordings cannot account for all 24-h activities, thus negating the influence of sedentary time and daily light intensity activity. Modern-day studies using objective measures of PA are highly controversial in the description of PA, as well as reliable wear time of these objective devices to accurately assess PA behaviour. The aim of the research presented in this thesis was to ascertain the associations between seven-day objectively measured PA (expressed as time spent in four different metabolic equivalent of task (MET) categories), cardiovascular disease risk factors (24-h ambulatory blood pressure and central obesity), chronic stress (General Health Questionnaire total score and serum cortisol) and DNA damage (leukocyte telomere length) in a cohort of African and Caucasian school teachers recruited from the Dr Kenneth Kaunda Education District in the North West Province of South Africa. All parameters were objectively measured (the GHQ was only added for thoroughness on measures of cognitive perceived stress) in the study population.

The Africans (n=96) were younger than the Caucasians (n=107) (48.33 versus 51.06 years, $p=0.024$), but presented with slightly higher waist circumferences, significantly higher 24-h ambulatory systolic blood pressure (SBP, $p\leq 0.000$), diastolic blood pressure (DBP, $p\leq 0.000$) and mean arterial pressure (MAP, $p\leq 0.000$); significantly higher perceived stress scores (GHQ total scores, $p=0.001$) and significantly shorter telomeres ($p\leq 0.000$). The hypertensive participants in the total group (Africans and Caucasians combined) recorded 2.2 hours (12.4%) more daily awake sedentary time than the normotensive participants ($p=0.004$) and sedentary time was also a slightly better predictor of hypertension than moderate and vigorous activity time (Odds ratio=1.00, $p=0.006$). Irrespective of race and sex, 24-h SBP and DBP measurements were respectively associated with daily awake sedentary time ($\beta=0.17$, $p=0.018$ and $\beta=0.18$, $p=0.020$), light activity time ($\beta=-0.15$, $p=0.043$ and $\beta=-0.16$, $p=0.041$), waist circumference ($\beta=0.45$, $p\leq 0.000$ and $\beta=0.33$, $p\leq 0.000$) and log serum gamma glutamyl transferase (γ -GT, alcohol use) ($\beta=0.18$, $p=0.018$ and $\beta=0.24$, $p=0.004$). An older age ($\beta=-0.28$, $p\leq 0.000$), higher alcohol consumption ($\beta=-0.21$, $p=0.003$) and increased central

obesity ($\beta=-0.17$, $p=0.017$) were associated with shorter telomeres. Attenuated cortisol levels ($\beta=-0.12$, $p=0.068$) showed a tendency towards associations with longer telomeres that may indicate possible cortisol down regulation to protect against DNA damage. Time spent in the different MET-categories showed no direct associations with either cortisol or telomere length. However, a sensitivity analysis indicated that daily light intensity activity time was significantly correlated with lower waist circumference ($r=-0.21$, $p=0.004$); a parameter associated with both cortisol ($\beta=-0.22$, $p=0.003$) and telomere length ($\beta=-0.17$, $p=0.017$).

The thorough recording of PA during the true awake time of 24-h cycles over a period of seven days ensured that the beneficial effect of light intensity activities, as well as the detrimental effect of sedentary time, was highlighted by this study. The average awake time of all ethnic and sex groups were around 17 hours per day, which was more than most previous studies using objective measures of PA. The exclusion of participants who did not comply through wearing the Actiheart for a full seven days ($n=143$, 40%) did, however, have a negative impact on sample size that may have affected the statistical power for uncovering some significant associations and the high participant burden of the Actiheart device became clear. Therefore, the researchers used the data of the full seven-day recordings to also determine the minimum number of consecutive days the Actiheart device could be worn to accurately estimate energy expenditure and PA. The two-day combination of Wednesday-to-Thursday did not differ from the weekly average TEE, as well as for all MET-categories in all ethnic and sex groups. This two-day combination is practically convenient and would lessen participant burden. Future researchers are urged to test this combination in other populations to standardize Actiheart wear time.

It can be concluded from the findings in this study that less daily awake sedentary time, more light intensity activity time, as well as lower alcohol consumption favour improved health as it is beneficial to 24-h ambulatory blood pressure and helps to maintain a healthy waist circumference, which ultimately influence telomere shortening. Furthermore, the two-day combination of Wednesday-to-Thursday seems to be sufficient to accurately estimate weekly energy expenditure and habitual PA with the Actiheart apparatus.

Key words: *Physical inactivity, cardiovascular disease risk factors, measures of physical activity, physical activity and perceived stress, physical activity and chronic stress, telomere shortening*

OPSOMMING

Die dosis-respons verhouding tussen fisieke aktiwiteit (FA), siekte en mortaliteit is hoofsaaklik ontleen aan self-gerapporteerde vraelyste in Westerse bevolkingsgroepe. 'n Groot beperking van self-gerapporteerde FA lê in die waarskynlikheid van metingsfoute en hierdie rapporterings kan nie verslag doen van alle 24-h aktiwiteite nie, dus negeer dit die invloed van sedentêre tyd en daaglikse lae-intensiteit aktiwiteit. Hedendaagse studies wat objektiewe metings van FA gebruik is hoogs kontroversieel in die beskrywing van FA, sowel as betroubare dratye van die objektiewe aparate om FA-gedrag akkuraat te kan bepaal. Die doel van die navorsing wat in hierdie proefskrif gerapporteer word, was om assosiasies te bepaal tussen sewe-dag objektief-gemete FA (uitgedruk as tyd bestee in verskillende metaboliese ekwivalent van take (MET) kategorieë), kardiovaskulêre siekterisikofaktore (24-uur ambulatoriese bloeddruk en sentrale obesiteit), kroniese stres (Algemene Gesondheidsvraelys (AGV) totale telling en serumkortisol) en DNA skade (leukosiet-telomeerlengte) in 'n subgroep van Afrika- en Kaukasiese onderwysers gewerf vanuit die Dr Kenneth Kaunda Onderwysdistrik in die Noordwesprovinsie van Suid-Afrika. Al die parameters is objektief gemeet (die AGV is bloot bygevoeg vir doeleindes van volledigheid vir metings van kognitiewe stres) in hierdie studiepopulasie.

Die Afrikane was jonger as die Kaukasiërs (48.33 teenoor 51.06 jaar, $p=0.024$), maar het gepresenteer met effens hoër middelomtrekke, beduidende hoër 24-h ambulatoriese sistoliese bloeddruk (SBD, $p\leq 0.000$), diastoliese bloeddruk (DBD, $p\leq 0.000$) en gemiddelde arteriële druk (GAD, $p\leq 0.000$); betekenisvol hoër kognitiewe strestellings (AGV totale tellings, $p=0.001$) en betekenisvolle korter telomere ($p\leq 0.000$). Die hipertensiewe deelnemers in die totale groep (Afrikane en Kaukasiërs gekombineerd) het 2.2 meer ure (12.4%) daaglikse wakker sedentêre tyd aangemeld as die normotensiewe deelnemers ($p=0.004$) en sedentêre tyd was ook 'n effens beter voorspeller van hipertensie as matige en hoë-intensiteit aktiwiteit (Odds ratio=1.00, $p=0.006$). Die 24-h SBD en DBD was onafhanklik van ras en geslag onderskeidelik geassosieer met daaglikse wakker sedentêre tyd ($\beta=0.17$, $p=0.018$ en $\beta=0.18$, $p=0.020$), ligte aktiwiteit (tijd) ($\beta=-0.15$, $p=0.043$ en $\beta=-0.16$, $p=0.041$), middelomtrek ($\beta=0.45$, $p\leq 0.000$ en $\beta=0.33$, $p\leq 0.000$) en log serum gamma-glutamieltransferase (γ -GT, alkoholgebruik) ($\beta=0.18$, $p=0.018$ en $\beta=0.24$, $p=0.004$). 'n Hoër ouderdom ($\beta=-0.28$, $p\leq 0.000$), hoër alkoholverbruik ($\beta=-0.21$, $p=0.003$) en verhoogde sentrale obesiteit ($\beta=-0.17$,

$p=0.017$) was geassosieer met korter telomere. Afgeplatte kortisolvlakke ($\beta=-0.12$, $p=0.068$) het 'n neiging na 'n assosiasie met langer telomere getoon wat moontlike afregulering van kortisolvlakke aandui ter beskerming teen DNA skade. Tyd spandeer in die verskillende MET-kategorieë het geen direkte assosiasies met kortisol of telomeerlengte getoon nie. Hoewel, 'n sensitiwiteitsanaliese het getoon dat daaglikse ligte-intensiteit aktiwiteit tyd is betekenisvol in verband gebring met 'n laer middelomtrek ($r=-0.21$, $p=0.004$); 'n parameter wat geassosieer was met beide kortisol ($\beta=-0.22$, $p=0.003$) en telomeerlengte ($\beta=-0.17$, $p=0.017$).

Die deeglike meting van FA gedurende die werklike wakkertyd van 24-h siklusse oor 'n tydperk van sewe dae, het verseker dat die voordelige uitwerking van ligte-intensiteit aktiwiteite, sowel as die negatiewe effek van sedentêre tyd, deur hierdie studie beklemtoon kon word. Die gemiddelde wakkertyd van al die etniese en geslagsgroepe was ongeveer 17 uur per dag, wat meer is as wat tydens vorige studies, wat van objektiewe metings van FA gebruik gemaak het, aangeteken is. Die uitsluiting van deelnemers wat nie die Actiheart vir 'n volle sewe dae gedra het nie ($n=143$, 40%), het ongelukkig 'n negatiewe impak gehad op die steekproefgrootte wat die statistiese kragtigheid van assosiasies kon beïnvloed en die Actiheart-apparaat se hoë las op deelnemers het ook duidelik geword. Dus het die navorsers die data van die volle sewe dae-opnames gebruik om ook vas te stel wat die minimum aantal opeenvolgende dae behoort te wees om die energieverbruik en FA akkuraat te kan meet met die gebruik van die Actiheart-apparaat. Die twee-dae kombinasie van Woensdag-tot-Donderdag het nie verskil van die weeklike gemiddelde totale energieverbruik nie, soos ook met die meting van al die MET-kategorieë in al die etniese en geslagsgroepe. Hierdie twee-dagkombinasie is prakties gerieflik en sal die deelnemerslas ietwat verlig. Toekomstige navorsing word aanbeveel om hierdie kombinasie te toets in ander populasies om die dratyd van die Actiheart te standaardiseer.

Gevolgtik blyk dit uit die bevindinge van hierdie studie dat minder daaglikse sedentêre wakkertyd, meer ligte-intensiteit aktiwiteit tyd en laer alkoholgebruik goed is vir verbeterde gesondheid, aangesien dit voordelig is vir 24-h ambulatoriese bloeddruk en help om 'n gesonde middelomtrek te handhaaf, wat uiteindelik telomeerverkorting beïnvloed. Verder blyk die twee-dagkombinasie van Woensdag-tot-Donderdag voldoende om weeklikse energieverbruik en FA akkuraat met die Actiheart-apparaat te bepaal.

Sleutelwoorde: *Fisieke onaktiwiteit, kardiowaskulêre siekterisikofaktore, metings van fisieke aktiwiteit, fisieke aktiwiteit en gepersipieerde stres, fisieke aktiwiteit en chroniese stres, telomeerverkorting*

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LIST OF ABBREVIATIONS

| | |
|--------|---|
| ACSM | American College of Sports Medicine |
| ADL | Activities of daily living |
| AEE | Activity energy expenditure |
| AEE | Activity energy expenditure |
| AHA | American Heart Association |
| ANCOVA | Analysis of covariance |
| ATP | Adenosine triphosphate |
| BMI | Body mass index |
| BP | Blood pressure |
| BSA | Body surface area |
| CAD | Coronary artery disease |
| CDC | Centres of disease control and prevention |
| CHD | Coronary heart disease |
| cm | centimetre |
| CVD | Cardiovascular disease |
| DBP | Diastolic blood pressure |
| DEE | Dietary-induced energy expenditure |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiography |
| EE | Energy expenditure |
| FFA | Free fatty acids |
| GHQ | General Health Questionnaire |

| | |
|-------------------------------|---|
| GPAQ | Global physical activity questionnaire |
| γ -GT | Gamma glutamyl transferase |
| H ₂ O ₂ | Hydrogen peroxide |
| HPA-axis | Hypothalamic-pituitary-adrenal-axis |
| HT | Hypertension |
| HR | Heart rate |
| HR max | Maximum heart rate |
| HRR | Heart rate reserve |
| ICC | Intra-class correlations |
| IPAQ | International physical activity Questionnaire |
| ISAK | International Society for Advancement of Kinanthropometry |
| Kcal | Kilocalories |
| Kg | Kilogram |
| Kg/km/h | Kilogram per kilometre per hour |
| kg/m ² | Kilograms per square meter |
| KJ/wk | Kilojoules per week |
| Km/h | Kilometre per hour |
| LIPA | Low-intensity physical activities |
| m ² | square meter |
| MAP | Mean arterial pressure |
| MET | Metabolic equivalent of task |
| mg/L | Milligrams per litre |
| Min | Minutes |
| ml | Millilitre |
| mmHG | Millimetre of mercury |

| | |
|-----------------------------|--|
| NAD ⁺ | Nicotinamide adenine dinucleotide oxidized |
| NADH | Nicotinamide adenine dinucleotide reduced |
| NCD | Non-communicable diseases |
| NO | Nitric oxide |
| NOS | Nitric oxide synthase |
| NWU | North-West University |
| O ₂ ⁻ | Superoxide |
| ONOO ⁻ | Peroxynitrite |
| PA | Physical activity |
| PAEE | Physical activity energy expenditure |
| PAL | Physical activity level |
| PBMC | Peripheral blood mononuclear cells |
| PDC | Pyruvate dehydrogenase complex |
| REE | Resting energy expenditure |
| ROS | Reactive oxygen species |
| RPE | Rate of perceived exertion |
| SABPA | Sympathetic activity and Ambulatory Blood Pressure in Africans |
| SBP | Systolic blood pressure |
| SNS | Sympathetic nervous system |
| SOD | Superoxide dismutase |
| TCA | Tricarboxylic acid |
| TEE | Total energy expenditure |
| THUSA | Transition and Health during Urbanisation of South Africans |
| U/L | Units per litre |
| USA | United States of America |

| | |
|---------------------|---------------------------------|
| VO ² max | Volume of maximum oxygen uptake |
| VO ² R | Volume of oxygen uptake reserve |
| WC | Waist circumference |
| WHO | World Health Organization |
| WHtR | Waist-to-height-ratio |
| YLL | Years to life lost |
| β-cell | Beta cell |
| °C | Degrees Celsius |



CHAPTER 1

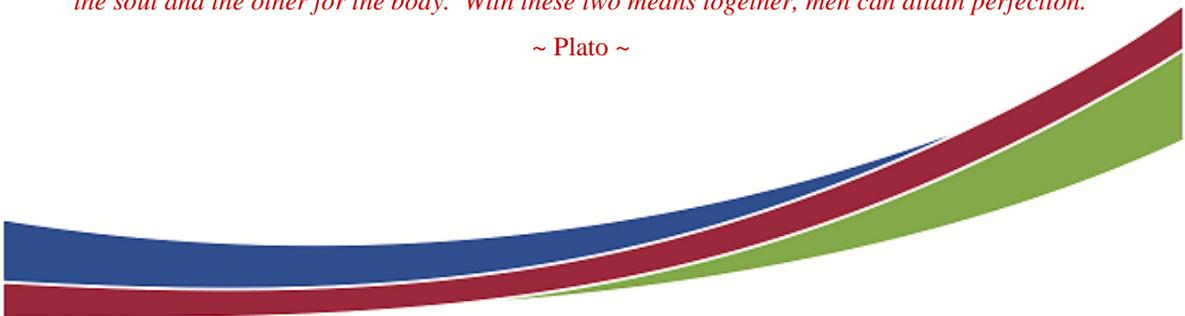
INTRODUCTION

- 1.1 PROBLEM STATEMENT
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In order for man to succeed in life, God provided him with two means, education and physical activity – one for the soul and the other for the body. With these two means together, men can attain perfection.

~ Plato ~



1.1 PROBLEM STATEMENT

Physical inactivity remains a worldwide public health concern in spite of substantial epidemiological evidence proving the benefits of regular physical activity (PA) for well-being (Akbarbartoori *et al.*, 2008:9; Assah *et al.*, 2011:493; Guthold *et al.*, 2008:491; Haskell *et al.*, 2007:1081; Reddigan *et al.*, 2011:1429). Globally, the proportion of years to life lost (YLL) due to non-communicable diseases (NCDs) increased from 38% in 2000 to 47% in 2012, (WHO, 2014:46). A raised blood pressure (BP) has been indicated to be the greatest contributor to NCDs, followed by tobacco use, raised blood glucose, physical inactivity, overweight and obesity (WHO, 2011a:16). It is projected that NCD-contributors will become greater mortality risks than HIV and AIDS in middle income countries by 2030 (WHO, 2011b:174). During the late 1970s, Seftel (1978:99) argued that coronary heart disease (CHD) was less common amongst the black South African population due to higher free living physical duties, as well as the more physical nature of their labour. However, the *Global burden of disease study* projected a rise in cardiovascular disease (CVD) in Africa from 1990 to 2020 (Murray & Lopez, 1997:1504). Results of more recent research confirm these projections as a positive rural-urban gradient in terms of the prevalence of CVD risk factors and metabolic diseases is observed in developing Sub-Saharan African countries (Assah *et al.*, 2011:494; Guthold *et al.*, 2008:489; Sobngwi *et al.*, 2004:775).

The dose-response relationship between PA and risk of cardiovascular and metabolic disease, as well as premature mortality, is well documented, indicating a more or less linear relationship of lower levels of risk with higher amounts of PA (Haskell *et al.*, 2007:1081; Warburton *et al.*, 2006:801). Combinations of moderate- and vigorous-intensity activity are recommended for three to five days of the week for maintenance of health. Moderate-intensity aerobic activity can be accumulated towards the 30-minute minimum requirement from bouts lasting no less than 10 minutes (Haskell *et al.*, 2007:1803). This recommended amount of aerobic activity is in addition to the routine activities of daily living such as self-care, shopping or casual walking, as these activities are usually of light intensity and less than ten minutes in duration. PA participation exceeding these minimum recommendations leads to additional improvements in health status, further reducing the risk of hypokinetic diseases (Haskell *et al.*, 2007:1084). A meta-analysis of large prospective cohort studies from January 1980 to December 2010 indicated that high levels of leisure time PA reduce CVD risk by 20% to 30%. Both leisure time and occupational PA of moderate intensities lower the CVD

risk by 10% to 20% (Li & Siegrist, 2012:401).

In the industrialised world, however, technology reduces the energy needed to perform activities of daily living and economic incentives are higher for sedentary than active work (Haskell *et al.*, 2007:1081). The latest World Health Organization (WHO) report showed that 62% of South Africans now live in urban areas (WHO, 2014:172). It was previously found that participants living in urban areas of South Africa are less likely to meet the existing PA guidelines (Guthold *et al.*, 2008:492). The previous WHO-report indicated that 46% and 57% of South African men and women, respectively, fail to adhere to the recommended PA guidelines (WHO, 2011b:176). In Cameroon, urban residents showed lower occupational, walking related and total PA levels, as well as lower free-living PA energy expenditure than rural dwellers (Assah *et al.*, 2011:495; Sobngwi *et al.*, 2002:1015). These urban habits were associated with a higher body mass index (BMI), BP and fasting blood glucose levels - especially in men (Sobngwi *et al.*, 2002:1015). Assah *et al.* (2011:493) indicated that PA energy expenditure is independently associated with prevalence of the metabolic syndrome.

The *Transition and Health during Urbanisation of South Africans* study (THUSA) in the North West Province of South Africa showed high physical inactivity levels in rural subjects, as well as in black women living in urban areas (Kruger *et al.*, 2002a:22). Although this study indicated body mass index rather than PA having a greater effect on diastolic BP, the researchers also stated that PA provided some protection against CHD, even in overweight subjects. Research in the developed world has shown that, even in the absence of improved aerobic fitness and reduced body fatness, increasing levels of PA over a long period of time may protect against metabolic diseases (Ekelund *et al.*, 2007:2104) and long term aerobic exercise is also regarded as an effective antihypertensive therapy (Ketelhut *et al.*, 2004:8).

Urbanisation is not only associated with decreases in PA, but is accompanied by insecurities and disruption, which contribute to additional psychological stress (Malan *et al.*, 2006a:305). In a review of the protective and damaging effects of stress, McEwen (2008:175) stated that the brain changes structurally and chemically in response to acute, as well as chronic stressors. In the event of a stressor, the brain responds by releasing chemical mediators, e.g. glucocorticoids or catecholamines that increase heart rate and BP for the “fight or flight” response. In other words, allostasis achieves homeostasis by means of the neuro-endocrine responses of the hypothalamic-pituitary-adrenal (HPA) axis, as well as the sympathetic

nervous system (SNS) (McEwen, 2008:176; Tsatsoulis & Fountoulakis, 2006:197). In the case of psychological stress, however, this increased metabolic energy is not used physically for “fight-or-flight” and are restored in the body, leading to glucocorticoid and catecholamine excess. In other words, allostatic overload occurs and the autonomic nervous system and hypothalamic-pituitary-adrenal axis responses are not “turned off” and the secretory end product of the HPA-axis, cortisol, remains high. Additional wear and tear of the cardiovascular system takes place, consequently resulting in, for example, insulin resistance, visceral obesity, dyslipidemia, hypertension and left ventricle hypertrophy (Björntorp, 2001:73).

Literature also suggest that the adrenal gland is hypoactive in some stress-related states and due to down regulation of the cortisol receptors, hypocortisolism in chronic stress conditions may occur (Fries *et al.*, 2005:1011; Heim *et al.*, 2000:2). Heim *et al.* (2000:1) indicated that a persistent lack of cortisol availability may promote an increased vulnerability for the development of stress related bodily disorders such as fibromyalgia. Hellhammer *et al.* (2004:11) found that although hypocortisolemic subjects scored high on measures of depression, perceived stress and physical complaints, they did not show allostatic load. This indicates that a hypocortisolemic stress response may have a protective role in cardiovascular and metabolic disorders (Hellhammer *et al.*, 2004:8).

Physical inactivity and high fat diets are common features of modern society, which intensify stress-related allostatic load, creating the “stress-induced-exercise-deficient-phenotype” and consequently an increased risk for cardiometabolic and stress-related disease (Hawley, 2004:384; Tsatsoulis & Fountoulakis, 2006:202). Individual behaviours that may reduce allostatic overload include the improvement of the quality and quantity of sleep, maintaining a healthy diet and engaging in regular PA (McEwen, 2008:181). A study of the effects of physical exercise on depression and neuroendocrine stress hormones indicated a significant reduction in 24-h urinary cortisol secretion after an eight-week jogging programme. The researchers concluded that regular physical exercise has a variety of benefits for physiological and psychological wellbeing in adolescent females with depressive symptoms (Nabkasorn *et al.*, 2005:182). In a study by Rimmele *et al.* (2007:627), it was found that trained men exhibited significantly lower salivary free cortisol levels and heart rate responses to a psychosocial stressor compared with untrained men. However, in another study only elite sportsmen showed consistently lower heart rate and cortisol responses compared with

untrained men, whereas amateur sportsmen showed lower heart rates but similar cortisol responses compared to untrained men. This implies that the level of PA differentially influences the physiological and psychological reactivity to psychosocial stress (Rimmele *et al.*, 2009:196).

In recent years, the research trend shifted towards establishing the link between neuroendocrine dysfunctions, morbidity and premature mortality. Telomere lengths are thought to be a pathway by which chronic stress and psychological stress responses are linked to disease pathogenesis (Butt *et al.*, 2010:24; Fitzpatrick *et al.*, 2006:19; Gilley *et al.*, 2008:32). Telomeres are deoxyribonucleic acid (DNA) protein complexes that cap chromosomal ends and become shorter each time a cell divides and, if not restored once crucial lengths are reached, the protective capping then no longer operates. This leads to either cell death (apoptosis), replicative senescence or to a malignant tumour cell (Monaghan & Haussmann, 2006:49). Although controversial, factors contributing to accelerated telomere shortening and the consequential aging related diseases include chronic psychological stress, smoking, obesity, diets high in polyunsaturated trans fatty acids, as well as low and vigorously high PA levels (Cassidy *et al.*, 2010:1275; Epel *et al.*, 2004:17313; Ludlow *et al.*, 2008:1767; Parks *et al.*, 2009:555). Several studies indicated that participation in regular moderate or vigorous levels of PA were associated with attenuation in telomere erosion or to buffer the detrimental effects of chronic stress on cellular longevity (Cherkas *et al.*, 2008:157; Ludlow *et al.*, 2008:1769; Ponsot *et al.*, 2008:472; Puterman *et al.*, 2010:e10837). Cherkas and colleagues reported the interesting results that the telomere lengths of individuals participating in leisure time PA for 199 minutes and more per week were found to be the same as sedentary individuals ten years younger (Cherkas *et al.*, 2008:156). As in the case of CVD risk factors and neuroendocrine response overload, a moderate physically active lifestyle is reported to have a positive effect in leukocyte telomere dynamics (Cherkas *et al.*, 2008:157; Ludlow *et al.*, 2008:1767; Puterman *et al.*, 2010:10839). This is probably due to the buffering effect of PA on perceived stressors (Puterman *et al.*, 2010:10839).

Ethnic differences have been reported for perceived stress biomarkers, as well as telomere length (Boyle *et al.*, 2007:2486; Zhu *et al.*, 2011:217). Many studies in sub-Saharan Africa have focused on the perceived stress of urbanization and the subsequent cardiovascular and neuroendocrine responses (Kruger *et al.*, 2002a:16; Kruger *et al.*, 2002b:422; Malan *et al.*,

2006b:158; Malan *et al.*, 2008:323; Sobngwi *et al.*, 2002:1009; Sobngwi *et al.*, 2004:769). PA questionnaires, known for various biases, are mainly used for associations with cardiovascular- and cardio-metabolic parameters. Although in one study the researchers tried to minimize the human error of self-reported questionnaires by developing questionnaires more suitable for the African population (Kruger *et al.*, 2002a:16), education level and perception of exercise intensity still hinder validity. Using different questionnaires also complicates comparison between studies and within different ethnic groups. Also, even in the case where the same questionnaires were used, human perception and education level influenced the results. This was indicated by the number of questionnaires being excluded because of unrealistic reports of PA adherence, for example, more than 133 hours per week (Sobngwi *et al.*, 2002:1009).

Available data on the PA dose-response relation have primarily been obtained from observational studies using self-report questionnaires conducted mainly in populations from North America, Australasia, and Europe (Li & Siegrist, 2012:403; Shimora & Lee, 2010:750). In their meta-analysis, Li and colleagues stated that evidence on the protective effects of regular PA on CVD is badly needed in rapidly developing countries (Li & Siegrist, 2012:403). Therefore, the research questions to be answered by this study are, firstly, what is the association between seven-day objectively measured habitual PA and ambulatory BP in a cohort of African and Caucasian teachers? Secondly, what is the association between seven-day objectively measured habitual PA, chronic stress and telomere length in a cohort of African and Caucasian teachers? Lastly, what is the minimum number of consecutive days the Actiheart device could be worn to accurately estimate energy expenditure and seven-day habitual PA in an African and Caucasian teachers' cohort? The research presented in this thesis is nested in the follow-up data of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study. The cohort profile of the SABPA study is well explained by Malan and colleagues (Malan *et al.*, 2014).

The diverse South African population calls for the use of objective measures to assess PA behaviour. Objective measurement of habitual PA during total awake hours provides a more reliable estimate of sedentary behaviour, as well as incidental light activity. To the knowledge of the authors, this is the first study to use objectively measured habitual PA (expressed as daily awake time spent in different MET-categories) obtained during true daily awake time for associations with physiological and biochemical parameters in two different

ethnic groups that are economically homogeneous. This study will serve as groundwork for education in lifestyle changes and intervention strategies which include PA in urban communities of South Africa. The results of this study will also serve as an objective measure for comparison between ethnic groups and will clarify for future research whether the Actiheart device should necessarily be worn for a total of seven days, as the participant burden of this device was shown to be quite high.

1.2 OBJECTIVES

The objectives of this study are to:

1. Assess the association between seven-day objectively measured habitual PA and ambulatory BP in a cohort of African and Caucasian teachers.
2. Determine the association between seven-day objectively measured habitual PA, chronic stress and leukocyte telomere length in a cohort of African and Caucasian teachers.
3. Ascertain the minimum number of consecutive days the Actiheart device should be worn to reliably estimate weekly energy expenditure and habitual physical activity in African and Caucasian teachers.

1.3 HYPOTHESES

The study is based on the following hypotheses:

1. Increased daily awake time spent in moderate and vigorous intensity habitual physical activities and decreased sedentary time will have a significant negative association with ambulatory BP in a cohort of African and Caucasian teachers.
2. African and Caucasian teachers who spend less daily awake time sedentary and more daily awake time doing moderate to vigorous intensity habitual physical activities will present with lower chronic stress levels and longer leukocyte telomere lengths.
3. The Actiheart device should be worn for a minimum of two consecutive weekdays, along with both days of the weekend to reliably estimate weekly energy expenditure and habitual physical activity behaviour in a cohort of African and Caucasian teachers.

This thesis is presented in article format and the three research articles (chapters 3-5) were written in accordance with the guidelines of the chosen journals for submission (including reference styles), whilst chapters 1, 2 and 6 were written in accordance with the NWU-guidelines. A schematic presentation of the structure of the dissertation is presented in figure 1.1.

1.4 STRUCTURE OF THE THESIS

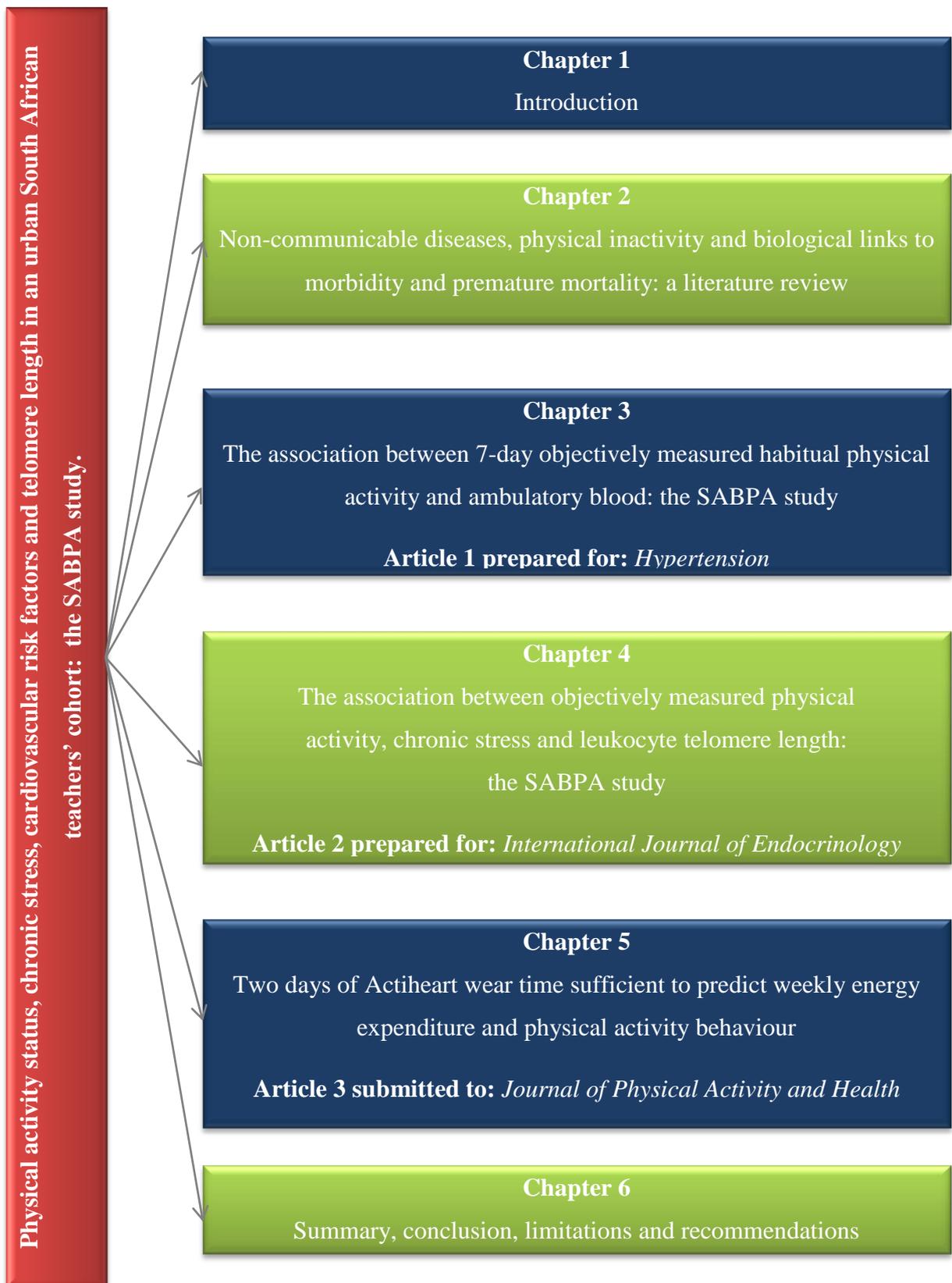


Figure 1.1: A schematic presentation of the structure of this thesis

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CHAPTER 2

Non-communicable disease risk, physical inactivity and biological links to morbidity and premature mortality: a literature review

2.1 INTRODUCTION

2.2 NON-COMMUNICABLE DISEASES

2.2.1 Non-communicable disease statistics and associated risk factors: a global picture.

2.2.2 Non-communicable disease statistics and associated risk factors: a South African picture.

2.2.3 Physical inactivity as a modifiable risk factor

2.3 PHYSICAL ACTIVITY

2.3.1 Physical activity: Definition and guidelines

2.3.2 Measures of physical activity

2.3.2 Physical activity and health

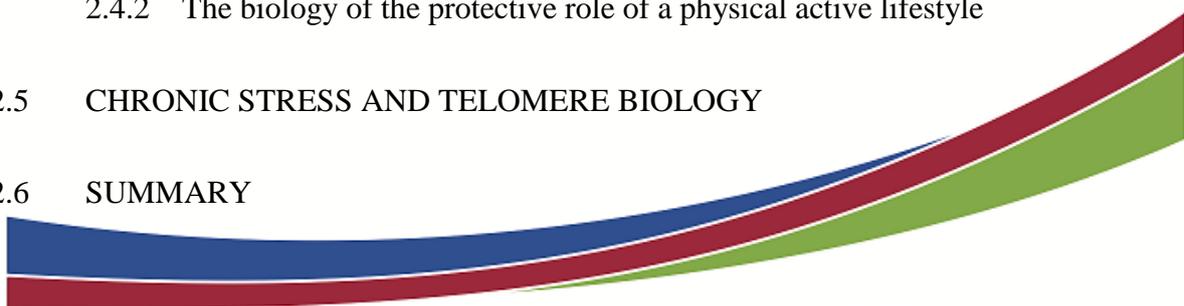
2.4 BIOLOGICAL MECHANISMS

2.4.1 Linking physical inactivity to morbidity

2.4.2 The biology of the protective role of a physical active lifestyle

2.5 CHRONIC STRESS AND TELOMERE BIOLOGY

2.6 SUMMARY



2.1 INTRODUCTION

The health benefits of physical activity (PA) for both body and mind have already been recognized by scientists and physicians in China and India 5000 years ago. Ancient Greek physicians, including Herodicus and Hippocrates, prescribed exercise to prevent and treat a variety of diseases (Bouchard *et al.*, 2012:24). Despite well-described PA guidelines for a better quality of life (Haskell *et al.*, 2007:1084), physical inactivity is currently one of the leading causes of non-communicable diseases (NCDs), resulting in 3.2 million annual deaths worldwide (6% of total annual global mortalities) (WHO, 2011^a:16). Blair (2009:1) argued physical inactivity to be the biggest public health issue of the 21st century. A physical inactive lifestyle and high fat diet are common features of the industrialized world today (Bauman *et al.*, 2008:122; Deaton *et al.*, 2011:S12, Gersh *et al.*, 2010:644). These unhealthy lifestyle choices make an enormous contribution to increased oxidative stress in the human body, a key element in the early onset of non-communicable diseases (NCD) and premature mortality (Camarillo-Romero *et al.*, 2012:3; Komatsu *et al.*, 2006:16; Robertson *et al.*, 2003:584).

Chronic exposure to increased physiological stressors, as observed in an urban-dwelling lifestyle, creates metabolic changes in the human body (for example increased cortisol and insulin secretion) – therefore chronic psychological stress exposure contributes to oxidative stress and eventually disease (Epel, 2009:13; Malan *et al.*, 2012:812). Research trends shifted during the late 21st century towards establishing the biological link between an unhealthy lifestyle and premature death. The rate of telomere shortening is a commonly used biomarker to identify excessive oxidative stress (Houben *et al.*, 2008:243) and although many studies have linked unhealthy behaviours such as physical inactivity, as well as cardiometabolic diseases to accelerated telomere shortening, most studies have failed to use objective measures for physical activity.

The global incidence of premature deaths due to behavioural risk factors such as tobacco use, physical inactivity, the harmful use of alcohol and unhealthy diets is alarming. The projection for Africa indicates NCD-deaths to exceed current death rates due to communicable diseases by 2030 (WHO, 2011^a:11). This calls for governments and policy-makers to implement preventative strategies. Promoting a physically active lifestyle is a cost-effective tool in NCD prevention (Fogelholm, 2010:219). However, Shimora and Lee

(2010:750) indicated that available data on the physical activity dose-response relation have primarily been obtained from observational studies using self-report questionnaires. These authors have also stated that there is a shortage of research on different ethnic groups.

2.2 NON-COMMUNICABLE DISEASES

2.2.1 Non-communicable disease statistics and associated risk factors: a global picture

The devastating consequences of the global NCD epidemic on societies and economies have urged the World Health Organization (WHO) to release the *Global Status Report on Non-communicable Diseases* during April 2011, a first of its kind. The main objectives of this release were, firstly, to map the epidemic of NCDs and analyse their determinants; secondly, to reduce the level of exposure of individuals and populations to the main risk factors through health promotion and primary prevention approaches; and lastly, to strengthen health care for those people already afflicted with NCDs by developing evidence-based norms and guidelines and cost-effective interventions (WHO, 2011^a:41-43). The hope is that the findings in this report would reinforce the urgency to better health in the 21st century.

According to the above-mentioned report, NCDs accounted for 63% (36 million) of the total global mortalities (57 million) during 2008, with 44% of these deaths being premature (before the age of 70) (WHO 2011^a:10). Nearly 80% of these deaths occurred in low-to-middle-income countries, except for Africa, where communicable diseases still contribute most to mortality rates (WHO 2011^a:9). However, age-standardized NCD mortality rates were the highest for all ages in the African Region (844 per 100 000 and 724 per 100 000 for males and females, respectively) (WHO 2011^a:9). Data from the WHO and Study of Global Aging and Adult Health (SAGE) indicated high prevalence rates of hypertension in people 50 years and above between 2007 and 2010 in low and middle-income countries (China, Ghana, Mexico, India, the Russian Federation and South Africa), with South Africa demonstrating the highest prevalence of 78% (Lloyd-Sherlock *et al.*, 2014:126). The WHO projections also show that, of the six WHO-regions, the greatest increases in death by NCDs between 2010 and 2020 would be in Africa, South-East Asia and the Eastern Mediterranean, with no increases projected for the European Region (WHO, 2011^a:1). In some African nations,

NCD-deaths are projected to exceed communicable, maternal, perinatal and nutritional diseases by 2030.

Cardiovascular diseases (CVD) contribute to almost half of the global NCD mortalities; followed by cancers, respiratory diseases (including asthma and chronic obstructive pulmonary diseases) and diabetes (WHO 2011^a:9). Figure 2.1 indicates the percentage contribution of the four main NCDs to the 36 million mortalities globally (compiled from WHO, 2011^a:9).

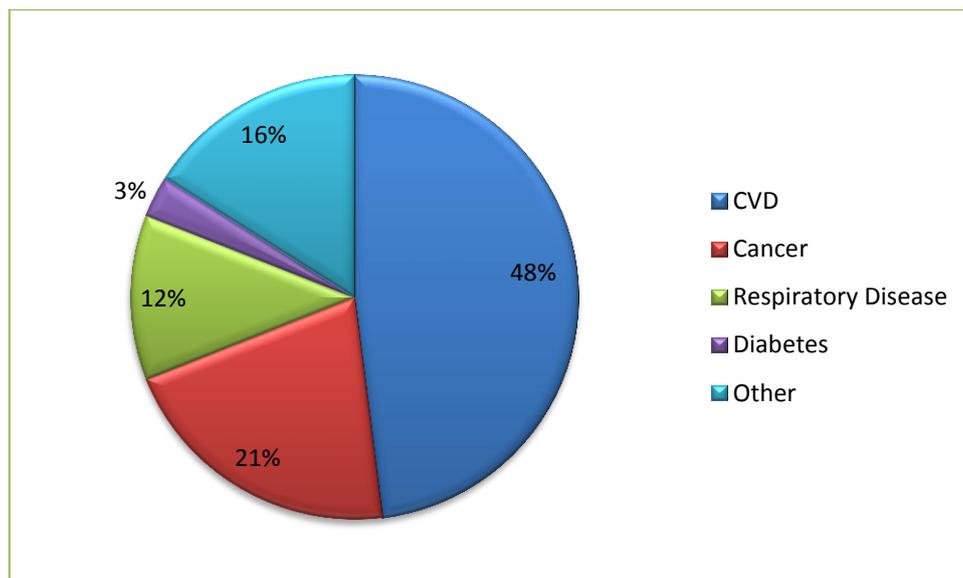


Figure 2.1: Percentage disease contributions to the 36 million global NCD deaths

As populations age, annual NCD deaths are projected to increase to 52 million globally by 2030 (WHO, 2011^a:11). Projections of global mortalities and burden of diseases from 2002 to 2030 by Mathers and Loncar (2006:2023) listed the ten leading causes of death worldwide by 2030 as follow: **ischaemic heart disease** (13.4% of total deaths); cerebrovascular disease (10.6%); HIV and AIDS (8.9%); chronic obstructive pulmonary disease (7.8%); lower respiratory infections (3.5%); trachea, bronchus and lung cancers (3.1%); diabetes mellitus (3.0%); road traffic accidents (2.9%); perinatal conditions (2.2%) and stomach cancer (1.9%).⁹⁸

The risk factors with the greatest contributions to the global mortality rates are: **raised blood pressure (13%), tobacco use (9%), raised blood glucose (6%), physical inactivity (6%) and overweight and obesity (5%)**. The four major behavioural risk factors (lifestyle

factors) associated with NCDs are: **tobacco use, physical inactivity, unhealthy diets and the harmful use of alcohol** (WHO, 2011^a:16).

An estimated 6 trillion **cigarettes** are consumed globally each year, causing about 71% of all lung cancer deaths, 42% of chronic respiratory diseases and 10% of CVD – in total accounting for 6% of all female and 12% of all male deaths globally (WHO, 2011^a:17). As little as 10% of the global population is fully protected by any of the tobacco demand-reduction measures, indicating inadequate commitment of governments, non-health sectors and key stakeholders to intervention strategies (WHO 2011^a:vii). The highest prevalence of smoking can be found in the European Region (29%), while the lowest prevalence is in the African Region (8%) (WHO, 2011^a:18).

The prevalence of **physical inactivity** (less than 150 minutes of moderate activity or 75 minutes of moderate-to-vigorous activity per week in addition to activities of daily living) was almost double in high-income countries (41% of men and 48% of women) compared to low-income countries (18% of men and 21% of women) (WHO, 2011^a:19). People who do not participate in regular physical activity have a 20-30% increased risk of all-cause mortality compared to those who meet the weekly physical activity recommendations (WHO, 2011^a:18).

The **harmful use of alcohol** is a major risk factor for NCDs such as CVD, certain cancers and liver disease, resulting in 3.8% of annual global deaths (WHO, 2011^a:19). The global consumption per capita was an estimated average of 6.0 litres in 2008, being more than double (± 10 litres) in middle-to-high income countries (such as South Africa) compared to low, and low-middle income countries ($\pm 3-4$ litres). **Unhealthy dietary habits** such as inadequate fruit and vegetable intake, high salt intake (more than 5 grams per day) and a diet high in saturated fats and trans-fatty acids, contribute to cardiovascular disease, certain cancers (especially stomach and colorectal cancers), overweight or obesity and type-2 diabetes (WHO, 2011^a:20-31, 41).

Table 2.1 indicates global mortalities due to unhealthy lifestyle choices (compiled from WHO, 2011^a:17-21). Note how physical inactivity was indicated as the second largest contributor to global mortalities of the leading behavioural risk factors. South Africa has previously been rated as the country with the third highest prevalence of physical inactivity (Guthold *et al.*, 2008:491).

Table 2.1: Annual global mortalities linked to behavioural risk factors

| Lifestyle factor | Mortalities |
|--|---------------------------------|
| Tobacco use | 6 million ^{*†} |
| Physical inactivity | 3.2 million deaths [†] |
| Harmful alcohol use | 2.3 million [‡] |
| Unhealthy diet (low fruit and vegetable consumption) | 1.7 million [†] |

*Tobacco mortalities from direct consumption and exposure to second-hand smoke, [†]2008 death statistics, [‡]2004 death statistics

2.2.2 Non-communicable disease statistics and associated risk factors: a South African picture

As mentioned earlier, physical inactivity (the fourth leading cause of NCDs) is much higher in high-income countries compared to low-income countries and South Africa is classified as an upper-to-middle-income country according to the previous WHO report (WHO 2011^b:174). The proportion of NCD mortalities under the age of 60 years in upper-to-middle-income countries is close to 20% for women and over 30% for men (WHO, 2011^b:6). Projections for the ten leading causes of death by 2030 for middle-income are as follows: cerebrovascular disease (14.4% of total deaths); ischaemic heart disease (12.7%); COPD (12.0%); HIV and AIDS (6.2%); trachea, bronchus and lung cancers (4.3%); diabetes mellitus (3.7%); stomach cancer (3.4%); hypertensive heart disease (2.7%); road traffic accidents (2.5%) and finally liver cancer (2.2%) (Mathers & Loncar, 2006:2023). Note how ischaemic heart disease alone, as well as total NCD-contributors will become a greater mortality risk than HIV and AIDS.

During the late 1970s, Seftel (1978:99) argued that coronary heart disease (CHD) was less common amongst the black South African population due to higher free-living physical duties, as well as the more physical nature of their labour. However, the latest WHO-report indicates that 62% of the South African population now lives in urban areas (WHO, 2014:172) and the transition from rural to urban settings in South Africa may contribute to behaviours characterised by those of the industrialized world (Vorster *et al.*, 2005:488). In other words, these urban dwellers would be less likely to walk long distances for basic needs and more likely to adopt the unhealthy lifestyle of a modern world. Projections from the

Global burden of disease study indicated a rise in CVD in Africa from 1990 to 2020 (Murray & Lopez, 1997:1504). Results of more recent research confirm the above mentioned projections, establishing a positive rural-urban gradient in terms of cardiovascular risk factors and metabolic diseases prevalence observed in developing Sub-Saharan African countries (Assah *et al.*, 2011:494; Guthold *et al.*, 2008:489; Sobngwi *et al.*, 2002:1014; Sobngwi *et al.*, 2004:775).

The *Non-communicable Disease Country Profiles* of the WHO provides estimates on the burden of NCD mortalities, prevalence and trends of major risk factors, as well as a country's capacity to respond to the NCD crisis (WHO, 2011^b:5). Adjusted estimates in this report were based on data provided by countries to the WHO or obtained through a review of published and unpublished literature. The criteria for inclusion in the estimation analysis stipulated that data had to represent a random sample of the general population of the country, provide a clear indication of the methods, sample size, as well as risk factor definition. Adjustments were made to ensure that an equal indicator could be reported for a standard year (2008) in all countries (WHO, 2011^b:14). Table 2.2 define the major risk factors for morbidity and inclusion in this WHO report (compiled from WHO, 2011^b:13).

Table 2.2: Risk factor definitions of the WHO NCD country profiles

| Definition of risk factors | |
|------------------------------------|--|
| Daily tobacco use (smoking) | % of population ≥ 15 years of age who smoke on a daily basis |
| Physical inactivity | % of population ≥ 15 years of age participating in less than 30 minutes of moderate activity 5x/week OR less than 20 minutes of vigorous activity 3x/week |
| Raised blood pressure | % of population ≥ 25 years of age with a SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg. |
| Raised blood glucose | % of population ≥ 25 years of age with fasting plasma glucose ≥ 7.0 mmol/L |
| Overweight | % of population ≥ 20 years of age with a BMI ≥ 25 kg/m ² |
| Obesity | % of population ≥ 20 years of age with a BMI ≥ 30 kg/m ² |
| Raised cholesterol | % of population ≥ 25 years of age with a total cholesterol ≥ 5 mmol/L |

South Africa showed a total NCD mortality rate of 190 500 (92 400 for men and 98 100 for women) during 2008, with CVD as leading contributor (11%), followed by cancers (7%), diabetes (3%) and respiratory disease (3%). NCD deaths accounted for 28% of the total mortality rate in South Africa. The South African statistics presented in Table 2.3 indicate an alarmingly high rate of physical inactivity, as well as cardiometabolic risk factors, especially the prevalence of hypertension (compiled from WHO, 2011^b:176). Findings from a study by Lloyd-Sherlock *et al.* (2014:122) indicated alarmingly low levels of hypertension awareness in low and middle income countries (including South Africa), with inadequate levels of treatment and control.

Table 2.3: Estimated prevalence rates of behavioural and metabolic risk factors in the South African population

| | Males (%) | Females (%) | Total (%) |
|-------------------------------------|------------------|--------------------|------------------|
| Behavioural risk factors | | | |
| Daily tobacco smoking | 21.2 | 7.0 | 14.0 |
| Physical inactivity | 46.4 | 55.7 | 51.1 |
| Cardiometabolic risk factors | | | |
| Raised blood pressure | 43.1 | 41.4 | 42.2 |
| Raised blood glucose | 10.3 | 11.0 | 10.6 |
| Overweight | 58.5 | 71.8 | 65.4 |
| Obesity | 21.0 | 41.0 | 31.3 |
| Raised cholesterol | 31.3 | 36.5 | 34.0 |

2.2.3 Physical inactivity as a modifiable risk factor

The *International Prevalence Study on Physical Activity* (Bauman *et al.*, 2009:6), which compared the physical activity behaviours of the adults in 20 countries (n = 52 746, aged 18-65 years) by means of the International Physical Activity Questionnaire, Short form (IPAQ-S) indicated that the majority of adults at least showed a moderate amount of physical activity participation. Walking, as a means of physical activity, contributed substantially (>30%) to physical activity statistics for countries with high, as well as those with low levels of physical

activity. More than half of the males in twelve of the participating countries and more than half of the females in fourteen countries did, however, not achieve the high physical activity threshold (Bauman *et al.*, 2009:2-8). These authors also found that participation in vigorous activity was the highest in Australia, Canada, New Zealand and the USA – all first-world countries with well-developed exercise and recreational facilities. This is, however, in contrast with the WHO-report which indicated high physical inactivity rates in high-income countries (WHO, 2011^a:19).

A 51-country health survey conducted by the WHO during 2002 to 2003 (n = 212 021 total participants, n = 2028 South African participants) ranked South Africa as having the third highest prevalence of physical inactivity, 43.0% and 46.6% for men and women respectively (Guthold *et al.*, 2008:491). This survey also showed that the prevalence of physical inactivity was higher for women and higher amongst older people, which is in accordance with the Bauman study (Bauman *et al.*, 2009:7). Participants living in urban areas were also less likely to meet the existing physical activity guidelines (Guthold *et al.*, 2008:492). These physical inactivity prevalence rates were even higher during 2008 for South Africa - 46.4% for men and 55.7% for women - according to the latest WHO report (WHO, 2011^b:176).

Of great concern is that in the previous WHO-survey, a country's ability to address and respond to NCD-threats was also assessed. The answer to the question as to whether an integrated or topic-specific policy, programme or action plan was operational in South Africa for different risk factors, was *YES* for all risk factors, including physical inactivity (WHO, 2011^b:176). Keeping in mind the statistics mentioned in the previous paragraph, it is maybe time to assess the success of these action plans, as the latest statistics clearly indicate a rise in the prevalence of physical inactivity. On the other hand, the increase in physical inactivity percentages could be an indication that one set of physical activity guidelines is not useful in the diverse South African community and that South Africa is maybe still undergoing major rural to urban transition.

2.3 PHYSICAL ACTIVITY

2.3.1 Physical activity: Definition and guidelines

The 1900s yielded many studies in an effort to describe PA patterns and determine the amount of PA needed for health benefits and longevity – some using self-reported occupational and leisure time physical activity as exposure variable, while others used objective measures, such as cardiorespiratory fitness measures and controlled exercise training experiments to determine dose-response relationships (Blair *et al.*, 1985:803; Morris *et al.*, 1958:1486; Paffenbarger & Lee, 1996:25; Pate *et al.*, 1995:406).

The American College of Sports Medicine (ACSM) and Centres for Disease Control and Prevention (CDC) were leaders in providing specific exercise recommendation with regular updates to follow – especially the 1995 recommendations were highly influential in the field of physical activity prescription and disease outcome (Blair *et al.*, 2004:915). During 2003 an expert panel, consisting of physicians, epidemiologists, exercise scientists and public health experts, was convened to review and update the PA guidelines for health enhancement published during 1995 by the ACSM and the CDC (Haskell *et al.*, 2007:1083). Table 2.4 (compiled from Haskell *et al.*, 2007:1083-1084) indicates the updated PA guidelines for maintenance of health in adults aged 18 to 65 years.

Table 2.4: Physical activity guidelines for healthy adults (18-65 years)

| Mode | Intensity | Duration | Frequency |
|-------------------------|------------------|--------------------|-------------------|
| Aerobic activity | Moderate | 30 minutes | 5 days / week |
| | (3-6METs) ** | | |
| | Vigorous | 20 minutes | 3 days / week |
| | (>6 METs) ** | | |
| Muscle strength | Amount | Repetitions | Frequency |
| (major muscle groups) | 8-10 exercises | 8-12 repetitions | 2 days / week |
| | | | (non-consecutive) |

** METs (metabolic equivalent of task): the ratio of a person's working / exercise metabolic rate to the resting metabolic rate (ml/kg/min) – 1 MET = 3.5ml/kg/min or 1kcal/kg/h; kcal/min: METs x 3.5 x body mass (kg) / 200

Physical activity is defined as *any bodily movement produced by skeletal muscles that results in an increase in metabolic rate over resting energy expenditure* (Bouchard *et al.*, 2012:12; Casperen *et al.*, 1985:127; Pate *et al.*, 1995:406). Therefore, not only structured exercise is recognised as physical activity, but leisure time activities, occupational work, as well as activities of daily living (ADL) (incidental activities, domestic activities and active commuting), are also included in this definition (Bouchard *et al.*, 2012:12). The recommendations for adults (18 to 65 years) from the ACSM and the American Heart Association (AHA) suggest moderate-intensity aerobic physical activity for a minimum of 30 minutes on five days each week (150 minutes of moderate activity per week or 495 METs minutes per week) or vigorous-intensity aerobic activity for a minimum of 20 minutes on three days per week (60 minutes of vigorous activity per week or 480 METs minutes per week) (Haskell *et al.*, 2007:1084). Moderate-intensity aerobic activity is equivalent to brisk walking that noticeably accelerates the heart rate and can be accumulated towards 30 minutes from 10-minute bouts during the day. Vigorous-intensity activity like jogging causes a substantial increase in heart rate and rapid breathing. The above recommendations are the minimum PA levels required for healthy adults to maintain health. Note that these recommended amounts of PA are in addition to routine activities of daily living of light intensity, as well as moderate intensity activities of less than ten minutes' duration (Haskell *et al.*, 2007:1084).

An obesity review by Bauman *et al.* (2008:122) indicated that leisure time physical activity alone may not be enough for obesity prevention and weight loss. This study suggested that *active living* should not only encourage leisure time PA, but also less sedentary occupational time, as well as active transport, especially in developing countries where energy expenditure is substantially reduced due to urbanization, industrialization and motor vehicle dependence. Levine *et al.* (2000:1453) documented that fidgeting-like activities (hand and feet tapping, arm and leg swinging, hair grooming gestures and computer work) during very low work intensities, resulted in substantial increases in energy expenditure in both lean and obese individuals. These authors argued that their findings may explain previous research which indicated that efforts to increase non-exercise activity showed benefits similar to that of an exercise programme.

Weight stable adults who participate in 30 minutes of aerobic activity per day are encouraged to increase their activity to 60 minutes per day and engage in resistance training and

flexibility exercises twice a week to ensure additional health benefits and a better quality of life (Blair *et al.*, 2004:918). To prevent age-related weight gain, an average physical activity level (PAL) of 1.75 is suggested, which is equivalent to approximately 60 to 90 minutes of moderate-intensity aerobic activity per day (Bouchard *et al.*, 2012:209). Good news, however, is that although the minimum requirements of PA per day suggest 30 minutes of moderately intensity activity, it could also be accumulated by bouts of ten minutes per session, contributing to cardiovascular health (Barr-Anderson *et al.*, 2011:91; Haskell *et al.*, 2007:1084).

Activities are categorised according to type or mode, intensity, frequency and duration (Bauman *et al.*, 2006:93). Absolute intensity is used to classify activities as light, moderate and vigorous and can be expressed as, the rate of oxygen consumption (ml/kg/min), the rate of energy expenditure (kcal/min) or the metabolic work rate relative to a standard resting metabolic rate (metabolic equivalent of task, METs). The energy cost of a person at rest (sitting comfortably or lying quietly) is 1 MET, that is equal to 3.5 ml/kg/min oxygen consumption or 1 kcal/kg/h (Ainsworth *et al.*, 2011:1577; Howley, 2001:365). The intensity of activity varies amongst different types of activities. Activities with an energy cost of less than three METs are seen as light intensity activities, 3-5.9 METs as moderate intensity activities and vigorous intensity activities have an energy cost equal and greater than six METs (Bouchard *et al.*, 2012:55). Brisk walking that noticeably accelerates the heart rate is generally used to describe moderate intensity aerobic activity and increases the body's metabolism 3-6 times above the resting level. An activity such as jogging that causes rapid breathing, sweating and a substantial increase in heart rate is seen as vigorous aerobic activity (Haskell *et al.*, 2007:1084). Slow walking is equivalent to 2.0 METs (light intensity activity), brisk walking (around 6.4 km/h) ranges between 3.3 and 5.0 METs (moderate intensity activity), while MET-values for jogging (7.2-11.2 km/h) range between 6.3 and 11.5 (Ainsworth *et al.*, 2000:500). Factors such as genetics, age, sex, body weight, physical fitness, and mechanical efficiency effect energy cost of activities (Browning *et al.*, 2006:397; Mahaudens *et al.*, 2009:1164; Ravussin & Bogardus, 1989:974).

Physical fitness is defined as *the ability to carry out daily tasks with alertness and vigour, without undue fatigue, and with enough energy reserve to meet emergencies or to enjoy leisure time pursuits* (Mosby's Medical Dictionary, 2009:1450). Any moderate intensity activity for a fit individual would be at a greater MET-level than for an unfit individual

(Bouchard *et al.*, 2012:58). Therefore, exercise for health is usually prescribed in relative intensity – in other words, a percentage of a person’s VO_{2max} , VO_2 -reserve or as a percentage of the estimated maximum heart rate of the individual. Table 2.5 gives an indication on how relative intensity differs according to fitness level (adapted from Howley 2001:367). Note how moderate intensity activity, which is recommended for health enhancement, is set at a level between 5.4 to 7.5 METs for a relatively fit individual, while only at 2.6 to 3.3 METs for an unfit person.

Table 2.5: Relative physical activity intensity for different fitness levels

| Intensity | RPE (Borg Scale) | % VO_2R % HRR | % HR max | % VO_{2max} | METs |
|---|-----------------------------------|---|-----------------|---------------------------------|----------------|
| Relative intensity in healthy fit individual with a VO_{2max} of 12 METs | | | | | |
| Very light | < 10 | < 20 | < 50 | < 27 | < 3.2 |
| Light | 10-11 | 20-39 | 50-63 | 27-44 | 3.2-5.3 |
| Moderate | 12-13 | 40-59 | 64-76 | 45-62 | 5.4-7.5 |
| Hard | 14-16 | 60-84 | 77-93 | 63-85 | 7.6-10.2 |
| Very hard to maximal | 17-20 | 85-100 | 94-100 | 86-100 | 10.3-12 |
| Relative intensity in healthy unfit individual with a VO_{2max} of 5 METs | | | | | |
| Very light | < 10 | < 20 | < 50 | < 36 | < 1.8 |
| Light | 10-11 | 20-39 | 50-63 | 36-51 | 1.8-2.5 |
| Moderate | 12-13 | 40-59 | 64-76 | 52-67 | 2.6-3.3 |
| Hard | 14-16 | 60-84 | 77-93 | 68-87 | 3.4-4.3 |
| Very hard to maximal | 17-20 | 85-100 | 94-100 | 88-100 | 4.4-5.0 |

RPE = rate of perceived exertion; % VO_2R = percentage volume of oxygen uptake reserve; % HRR = percentage of heart rate reserve; %HR max = percentage of estimated maximum heart rate; % VO_{2max} = percentage volume of maximum oxygen uptake; MET = metabolic equivalent of task

The updated *Compendium of Physical Activities* provides 821 activity codes of which 561 have measured MET-values ranging from 0.9 METs (for sleeping) to 23 METs (for running on a treadmill at 22.5 km/h) (Ainsworth *et al.*, 2011:1578). This compendium enables physicians and clinical exercise scientists (biokineticists) to incorporate the different domains

of PA (leisure-time, occupational, domestic and active commuting) (Bauman *et al.*, 2006:94) in the prescription of PA for healthy living, as the energy cost of different activities can easily be calculated. For example, the kilocalorie (kcal) cost of a 70 kg individual, sweeping at moderate effort (3.8 METs) equals: $3.8\text{METs} \times 70\text{kg} \times 0.5\text{h} = 133 \text{ kcal}$ or otherwise expressed 1.9 kcal/kg/h if divided by 70 (kg of body weight) (Ainsworth *et al.*, 2011:1578). This is especially useful in a country such as South Africa where activities of daily living differ so drastically between urban and rural living.

In the industrialised world of today, technology reduces the energy needed to perform activities of daily living and economic incentives are higher for sedentary than active work (Haskell *et al.*, 2007:1081) – thus creating a high-sedentary, low-activity pattern in many working adults. Bouchard (2012:55) stated that a significant amount of the 16-hour awake time per day (if assumed that eight hours are spent sleeping) is spent sedentarily or doing low-intensity physical activities (LIPA), which is not beneficial for health enhancement. For example, people with desk jobs can sit for six to seven hours (75% of the workday) with additional hours spent driving, watching television and doing LIPA such as cooking and performing household chores.

Bauman *et al.* (2006:94) stated that two other domains of PA, namely incidental energy expenditure (using the stairs instead of elevator) and sedentary behaviours (watching television and working on a computer) should be considered in the description of PA patterns. This call was strengthened by the findings of a review on sedentary behaviours that revealed that prolonged sitting periods compromise metabolic health, even when adults do meet the physical activity guidelines (*active couch potato phenomenon*) (Owen *et al.*, 2010:108). In the early 1700s, Ramazzini already noted that runners (messengers) did not suffer from many of the health problems in comparison to those of “sitting occupations”, for example, cobblers and tailors (as quoted by Bouchard *et al.*, 2012:24). As early as the 1950s, research of Morris and Crawford (1958:1495) reported that men doing physically active jobs (for example boiler-makers and dock labourers) had less CAD during middle age and the heart diseases in these men were less severe - probably due to low sedentary and high physical occupational PA patterns. It was further stated that the hearts of sedentary and light activity workers (for example school masters, bus drivers, postmen and carpenters) showed pathology similar to the hearts of workers doing heavy activity 10 to 15 years older.

Although the latest PA guidelines clearly state that the light, as well as moderate intensity activities of daily living, lasting less than ten minutes are not sufficient to contribute to health promotion (Haskell *et al.*, 2007:1804), the research of Healy *et al.* (2008:371) suggested replacing sedentary time with light-intensity daily activities to reduce central obesity and overall metabolic risk in adults (30 to 87 years old). This study found that time spent sedentarily has a stronger influence on waist circumference than moderate-to-vigorous-intensity physical activity. This is consistent with the work of Bankoski *et al.* (2011:501) on US adults that showed a strong association between sedentary time and metabolic risk, independent of PA. Many modern-day studies that employed questionnaires, as well as objective measures of PA, have emphasized the detrimental effect of sedentary time on cardiovascular- and cardiometabolic risk markers (Healy *et al.*, 2011:596; Stamatakis *et al.*, 2012:1335; Warren *et al.*, 2010^a:884). Although all these studies indicate that sedentary behaviour is harmful for health, the comparison of results is challenged by the varied definitions for PA, the differences in measuring tools used, as well as major variations in the wear time of devices used to objectively measure PA.

2.3.2 Measures of physical activity

Bauman *et al.* (2009:6) stated that international comparisons of key NCD risk factors, such as obesity and tobacco use, are possible, but comparisons of PA behaviours worldwide, are basically impossible due to the lack of globally used standardised and validated instruments for measurement of PA patterns. A key consideration when choosing a PA measurement tool is the reliability (indicating the reproducibility of an instrument – will the same results be obtained when the method is used by different independent assessors), the validity (indicating the ability of an instrument to measure what is supposed to measure) and lastly the responsiveness or sensitivity (indicating the ability of an instrument to detect change over time (Warren *et al.*, 2010^b:128). The doubly labelled water (DLW) technique is known as the gold standard for measuring an individual's EE. The rate of CO₂ production is reflected in this technique, which in turn can be used to estimate EE (Anslie *et al.*, 2003:686). Although this technique could be used for all age groups in most settings, sophisticated equipment is required for analysis and the high cost limits the testing of large groups (Anslie *et al.*, 2003:686).

Although self-report measures of PA, such as the IPAQ and GPAQ (Global Physical Activity Questionnaire), are standardized and validated (Armstrong & Bull, 2006:69; Craig *et al.*, 2003:1389), the contributors to measurement errors such as individual recall bias, daily and seasonal variability in PA patterns and different interpretations of especially intensity of activity due to differences in human perception and lack of education, could not be ignored (Bauman *et al.*, 2006:94). The study of Bauman and colleagues (2009:6), as well as the 51-country health survey conducted by the WHO during 2002 to 2003 (Guthold *et al.*, 2008:491) (see p.8), in which the validated self-report IPAQ short form was used, served as good efforts to compare PA behaviours within different countries; however, one should note the ethnic, cultural and level of education differences of countries selected for participation in these studies. It is especially these factors which hinder between-country comparisons and contribute to measurement errors. In developing countries (such as many sub-Saharan countries), it is especially the levels of education and human perception that hinder measurement of PA by means of questionnaires. This is clearly indicated in a Cameroon study where a large number of questionnaires had to be excluded because of unrealistic reports of PA adherence, for example, more than 133 hours per week of physical activity were reported (Sobngwi *et al.*, 2002:1009). The researchers in a South African study had to develop a questionnaire more suitable for the African population to minimize the human error of self-reported questionnaires (Kruger *et al.*, 2002:16), especially in rural areas where activities differ substantially from those used in questionnaires to calculate the physical activity indices.

Craig *et al.* (2003:1389) stated that the IPAQ is ideal to use in developed countries and urban areas of developing countries, but should be used with caution in rural areas, and amongst individuals with low literacy. The GPAQ was developed by the WHO to improve assessment of PA patterns in developing countries and a review by Armstrong and Bull (2006:69) indicated positive feedback from the 49 developing countries (including South Africa) that used the questionnaire in health surveys. Still, the use of PA questionnaires in South Africa is further complicated by the fact that this country has eleven official languages – thus, interviewers (translators) should not only be able to be fluent in a specific language, but should also interpret and explain the content of the questionnaire correctly to participants. Warren *et al.* (2010^b:131) clearly stated that validity results assessed in one population cannot be systematically extrapolated to other populations, ethnic groups or other geographical

regions. Also, all questionnaires show limitations in the measurement of both occupational and non-occupational sedentary behaviours (Clark *et al.*, 2009:13).

Objective measures such as pedometers, accelerometers, heart-rate monitors or combined accelerometer and heart rate monitors have widely been used in an attempt to eliminate the self-report method bias. In a systematic review to compare direct (objective) versus self-report measures for assessing PA-status in adults, Prince *et al.* (2008:70) concluded that no clear trends have emerged in the over- or under-reporting of PA through self-report compared to direct methods. A possible reason for under-reporting could be the fact that many self-report questionnaires do not include energy expenditure of activities lasting less than ten minutes in duration (Prince *et al.*, 2008:68). Over-reporting is likely to occur due to social desirability – especially in overweight and obese individuals (Prince *et al.*, 2008:69). Although direct measures such as pedometers and accelerometers are relatively inexpensive, these methods are unable to capture certain types of activities such as swimming (as most of the apparatus is not water-resistant) and upper extremity activities (as the devices are worn on the waist) (Prince *et al.*, 2008:68; Warren *et al.*, 2010^b:135).

In the combined accelerometer and heart rate monitors, the pros of the devices are merged, thereby opposing some of the disadvantages. For example, heart rate monitors are less accurate at low intensities to estimate energy expenditure, but accelerometers are highly effective at this level. Also, upper extremity exercises and non-wearing times are difficult to determine with the accelerometer, but in a combined device this will be eliminated due to the heart-rate component (Warren *et al.*, 2010^b:134). The Actiheart[®] (a combined accelerometer and heart-rate device) has been established as a valid and reliable device to correctly estimate energy expenditure in adults in free-living conditions, for humans at rest, as well as at low, moderate and vigorous intensity activities which vary in studies from house hold tasks to running and has been validated against DLW (Assah *et al.*, 2011^b:118; Barreira *et al.*, 2009:69; Brage *et al.*, 2005:568). This device is waterproof and does not need to be removed, except when replacing the electrodes – therefore total energy expenditure (TEE) can be measured, rather than only physical activity energy expenditure (PAEE) (Prince *et al.*, 2008:69; Warren *et al.*, 2010^b:134).

Contradicting research does, however exist, which indicated that the combined device alone is not useful in predicting activity energy expenditure of light intensity activities compared to

moderate-to-vigorous intensity activities (Crouter *et al.*, 2008:709). Spierer *et al.* (2011:659) even concluded that the Actiheart, which is much more expensive, fails to provide better estimates than the Actical for activities where acceleration of the pelvis is related to energy expenditure.

The accurate measurement of PA and energy expenditure is crucial to determine lifestyle behaviours and implement intervention strategies in the industrialized world. Research, however, gives no clear answer as to which method of estimating PA patterns in adults is advisable to use in all conditions. Warren and colleagues mentioned that the cost of an assessment method is inversely proportional to its accuracy (Warren *et al.*, 2010^b:129) – referring to self-report questionnaires as the least expensive, as well as the least accurate PA measurement tool and an objective measure such as direct room calorimetry as highly accurate, but extremely expensive and inconvenient. A researcher should consider factors such as the number of participants to be monitored, time period of measurements, finances available, skill of personnel, as well as cultural and geographical diversity to determine the preferred method of estimating energy expenditure (Ainslie *et al.*, 2003:395; Shephard, 2003:203; Warren *et al.*, 2010^b:131). The combined accelerometer and heart-rate method, such as the Actiheart, seems to be an effective objective measurement of energy expenditure, not only for structured exercise, but also in free-living conditions (Assah *et al.*, 2011^b:118; Barreira *et al.*, 2009:69; Brage *et al.*, 2005:568). It would therefore be ideal to use these devices in the diverse South African setting; however, the main disadvantage of such devices is the cost (Warren *et al.*, 2010^b:134).

2.3.3 Physical activity and health

The alarmingly high NCDs-prevalence worldwide, usually with concomitant increases in obesity and decreases in PA, merits priority attention to efforts committed to increasing PA levels in populations (Bauman *et al.*, 2006:92). A physically active lifestyle is known to reduce the risk of developing obesity, hypertension, coronary artery disease, type 2 diabetes, osteoporosis, depression, as well as breast- and colon cancer (Bassuk & Manson, 2005:1201; Thompson *et al.*, 2003:e43; Wessel *et al.*, 2004:1186; Wolin *et al.*, 2009:613; Yates *et al.*, 2010:294). Literature provides evidence which relates physical inactivity to the above-mentioned NCDs, as well as associated risk factors (Mora *et al.*, 2007:2116; Reddigan *et al.*, 2011:1429; Shimora & Lee, 2010:750). McGuire *et al.* (2009:1525) for example found that

physical inactivity predicts the likelihood of CVD beyond that of commonly measured cardiometabolic risk factors (smoking, cholesterol, glucose, blood pressure, waist circumference). These authors stated that their findings underscore the importance of obtaining a PA measure in the clinical setting to identify individuals with an increased risk of developing CVD. Ironically enough, it is this modifiable risk factor which shows increasing statistics in epidemiology papers.

The dose-response relationship between PA, the risk of developing CVD and premature mortality are all well-documented, indicating a linear relationship of lower levels of risk with higher amounts of PA (Haskell *et al.*, 2007:1081; Warburton *et al.*, 2006:801). A physical active lifestyle is therefore associated with longevity and a lower risk of all-cause mortality (Blair *et al.*, 1995:1097; Hamer & Stamatakis, 2009:156; Lee & Paffenbarger, 2000:295; WHO, 2011^a:18, 19).

A large prospective study initiated by the National Institutes of Health in America concluded that participation in 30 minutes of moderate intensity PA for more than three hours per week decreases the mortality risk by 27%, while 20 minutes of vigorous-intensity-activity three or more times per week were associated with a 32% reduction in the mortality risk (Leitzmann *et al.*, 2007:2459). This is in accordance with a study during the late 1900s, *The Harvard Alumni Health Study* (Lee *et al.*, 1995:1181), which revealed that vigorous-intensity physical activity (≥ 6 METs) is inversely related to mortality in middle-aged men – this is after potential cofounders such as smoking, hypertension, diabetes mellitus and early parental death were considered. However, this inverse relationship seems to taper at approximately 14 700 kJ/wk of total energy expenditure (TEE) or 12 600 kJ/wk of vigorous-intensity energy expenditure. A recent prospective study on individuals with stable coronary heart disease revealed reverse J-shaped PA associations, with higher major and non-fatal cardiovascular events, as well as higher cardiovascular and all-cause mortality rates in the subject, who never or rarely participated in PA, as well as in those with daily or five to six times per week participation in PA. The prognosis of participants who rarely or never engaged in PA was also worse than those who participated in moderate PA two to four times per week (Mons *et al.*, 2014:1046).

A meta-analysis of the association of PA with all-cause and cardiovascular mortality, which included nearly 900 000 participants amongst all included studies, indicated PA to have a 30-

50% risk reduction for cardiovascular mortality and 20-50% for all-cause mortality (Nocon *et al.*, 2008:244). These authors did, however, state that the largest risk reductions were indicated by studies that did not adjust for important cofounders. Also, consensus regarding the protective effect of a physically active lifestyle varies considerably due to the differing methods used to assess physical activity (self-reports and objective measures), as well as the heterogeneous manner by which PA levels is classified across studies – most studies using low, moderate and high groups, while some studies categorized in more subgroups. One should also keep in mind that most of the research on PA dose-response originated primarily from studies using self-report PA questionnaires and that the relation between PA and CVD risk in non-white populations are very limited (Shimora & Lee, 2010:746). Studies in which objective means of assessing PA were used seemed to show larger risk reductions, as participants tend to overestimate their levels of activity in self-reports and therefore minimising the true protective effect (Nocon *et al.*, 2008:245).

2.4 BIOLOGICAL MECHANISMS

2.4.1 Linking physical inactivity to morbidity

Physiological changes in the human body underlying the health enhancing benefits of regular PA include improved cardiovascular function such as a reduced heart rate, reduced blood pressure, improved endothelium-dependent vasodilatation and increased maximal myocardial oxygen uptake; metabolic benefits such as regulation of body weight, enhancement of insulin sensitivity, improved glucose tolerance through means of glycemic control, improved blood lipid profiles (decreased triglycerides and low-density lipoprotein and increased high-density lipoprotein); as well as favourable effects on inflammatory defence systems (Cornelissen *et al.*, 2011:955; Cornelissen & Faggard, 2005:673; Di Francescomarino *et al.*, 2009:807; Goto *et al.*, 2003:534; Ibanez *et al.*, 2005:665; Lira *et al.*, 2010:35; Ross *et al.*, 2004:789, Valkeinen *et al.*, 2010:554). The dose-response of different domains and intensity of PA and exercise remains highly controversial throughout literature.

The molecular mechanisms linking physical inactivity to the cardiometabolic disease risk are not fully understood; however, literature indicates that oxidative stress may be a mediating pathogenic factor for the development of disease (Ceriello & Motz, 2004:820). Unhealthy

behaviours, such as high fat diets and physical inactivity, which are common features of the technology driven industrialised world of today, contribute to oxidative stress which exploits the human body to disease and eventually mortality (Epel 2009:8). The metabolic mechanism by which oxidative stress increases with chronic over nutrition and physical inactivity is explained in a simplified schema below (Figure 2.2, compiled from various sources explained below the schema).

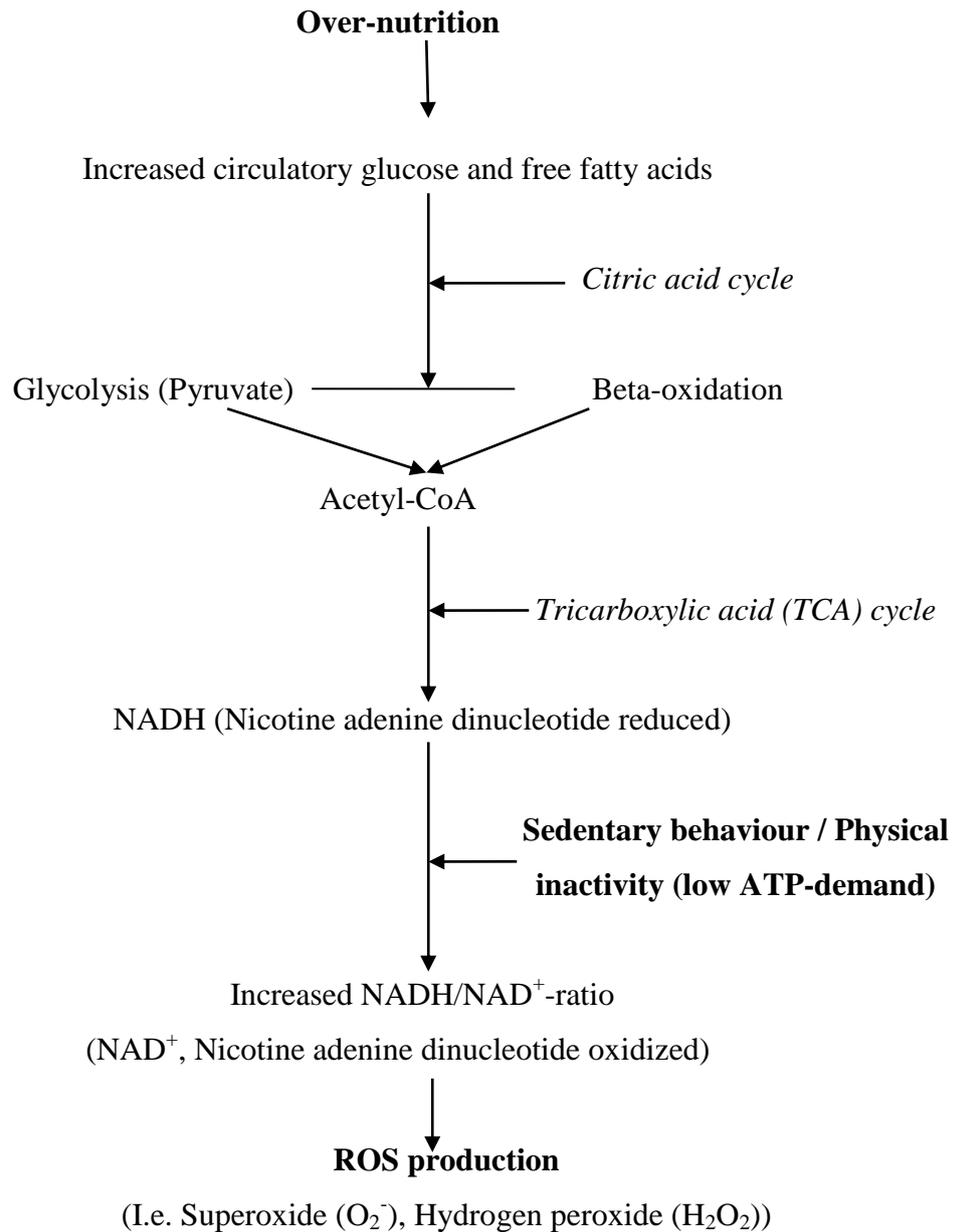


Figure 2.2: Simplified schematic presentation of ROS by chronic over-nutrition and physical inactivity

Over-nutrition results in elevated levels of circulatory glucose and free fatty acids (FFA) which overstimulate for instance the citric acid cycle activity. Glucose and FFA are respectively broken down by glycolysis (pyruvate) and beta-oxidation to provide acetyl-CoA and an increase of electron donors (such as NADH) from the tricarboxylic acid cycle (TCA-cycle) is stimulated. If the cellular ATP-demand is low due to a sedentary lifestyle, the acetyl-CoA does not enter the Krebs-cycle for adenosine triphosphate (ATP) synthesis through oxidative phosphorylation. This causes an increase in the NADH/NAD⁺-ratio in the mitochondria and the TCA-cycle then lowers the NADH supply to the mitochondrial respiratory chain (Ceriello & Motz, 2004:817; James *et al.*, 2012:433; Murphy, 2009:9).

The NADH-supply is, however, maintained by the pyruvate dehydrogenase complex (PDC) and malate dehydrogenase reactions, creating an increased mitochondrial proton gradient as NADH is not dissipated by oxidative phosphorylation (James *et al.*, 2012:432). These single electrons are then transferred to oxygen and free radicals or reactive oxygen species (ROS) are formed, for instance superoxide (O₂⁻), which in turn is catalysed by superoxide dismutase (SOD) to hydrogen peroxide (H₂O₂) (Ceriello & Motz, 2004:817; James *et al.*, 2012:431; Kodja & Hambrecht, 2005:193).

An increased production of ROS is associated with cardiovascular and cardiometabolic diseases, as oxidative stress leads to vascular endothelial cell dysfunction, β-cell dysfunction and muscle adipocyte. These dysfunctions eventually lead to vascular vasoconstriction and atherosclerosis, altered insulin secretion and insulin resistance, which all contribute to cardiovascular disease (Ceriello & Motz, 2004:820; Evans *et al.*, 2003:6).

Although the biological mechanism linking oxidative stress to disease is not yet fully understood, literature indicates that increased oxidative stress interferes with the protective role of nitric oxide (NO) which functions as an antioxidant, vasodilator, antiplatelet component and anti-adhesive component if produced in vascular endothelial cells (Gewaltig & Kojda, 2002:252). One of the most important reactive oxygen species, superoxide (O₂⁻), has been shown to interfere with the production of nitric oxide (NO). Drummond *et al.* (2000:352) reported that the expression and activity of endothelial Nitric Oxide Synthase (eNOS), the enzyme that generates the vasoprotective molecule NO, is increased if endothelial cells are exposed to H₂O₂. Normally, the concentration of superoxide dismutase (SOD) is much higher in vascular endothelial and smooth muscle cells than the

concentrations of NO - thus O_2^- is dismutated to H_2O_2 . In the case of ROS over-production, O_2^- is not only dismutated to H_2O_2 , but also reacts with the increased NO-concentrations to form peroxynitrite ($ONOO^-$) which has a strong oxidation potential (Drummond *et al.* 2000:352; Griendling & FitzGerald, 2003:1912). β -cells are especially sensitive to ROS as they are low in antioxidant enzymes such as glutathione peroxidase and superoxide dismutase. Therefore, an increased production of ROS by means of over-nutrition and a sedentary lifestyle eventually outweigh the protective role of NO (Figure 2.3 below, compiled from Ceriello & Motz, 2004:820).

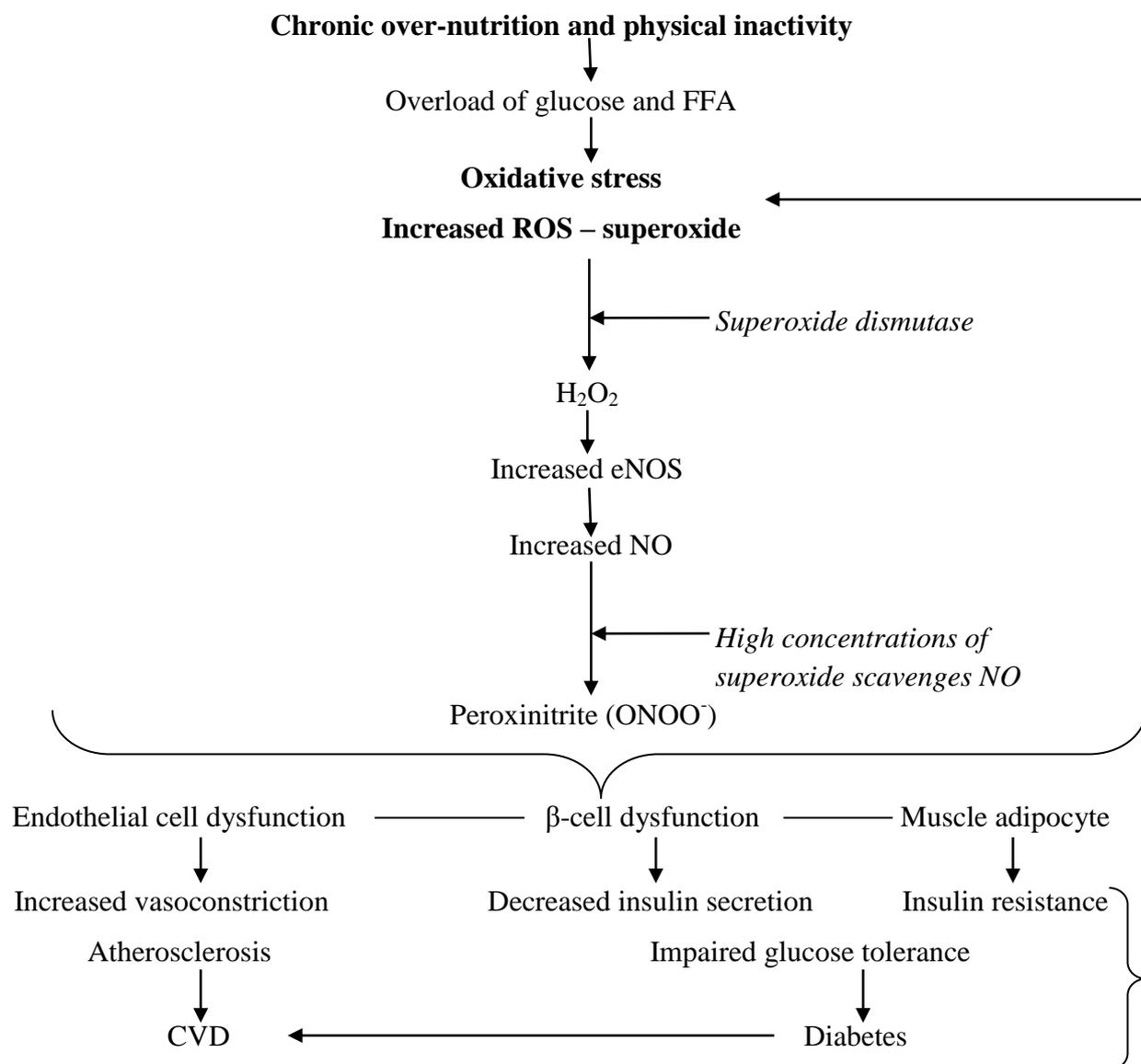


Figure 2.3: Schematic presentation of the pathogenic mechanism of physical inactivity and over-nutrition

2.4.2 The biology of the protective role of a physical activity lifestyle

Exercise increases the expression of extracellular superoxide dismutase (ecSOD), as well as eNOS in the vascular smooth muscle cells. This up-regulation of eSOD and eNOS results in a decrease in the superoxide levels and the formation of peroxynitrite in the vascular wall (Gewaltig & Kojda, 2002:256). In patients with coronary artery disease (CHD), it has been found that potentially atheroprotective vascular proteins (i.e. eNOS) and angiotensin receptor type 2 show up-regulation due to the physical forces induced by exercise training, while potentially atherogenic vascular proteins such as vascular smooth muscle NADH oxidase subunits and angiotensin receptor type 1 are down-regulated (Adams *et al.*, 2005:560). Other vascular adaptations to exercise include angiogenesis (an increase in the number of arterial vessels) and arteriogenesis (increase in the diameter of arterial blood vessels) of arterial blood vessels in skeletal muscle, as well as the myocardium (Kojda & Hambrecht, 2005:193).

Improved endothelium dependent vasodilatation was observed after a 12-week moderate intensity aerobic exercise programme (5 to 7 times per week) due to the increased NO-production (Goto *et al.*, 2003:532). NO-mediated remodelling of smooth muscle endothelium cells occur with long-term exercise training that results in a chronic increase in vessel diameter and normalization of shear stress (Maiorana *et al.*, 2003:1021). Elosua *et al.* (2003:331) found an increase in antioxidants such as glutathione peroxidase in whole blood, glutathione reductase in plasma, after a 16-week aerobic physical activity programme, with no significant increase in erythrocyte superoxide dismutase (eSOD). In a review of molecular mechanisms and vascular adaptations to exercise, Kojda and Hambrecht (2005:194) concluded that long-term physical activity improves endothelium-dependent vasodilation in response to physical forces on the blood vessel wall due to flow or acetylcholine infusion. These physical forces on blood vessels such as shear stress, transmural pressure and cyclic stretch increase during exercise, stimulating vascular endothelial cell adaptations (Gewaltig & Kojda, 2002:255; Kojda & Hambrecht, 2005:193) (see Figure 2.4 below compiled from above mentioned resources).

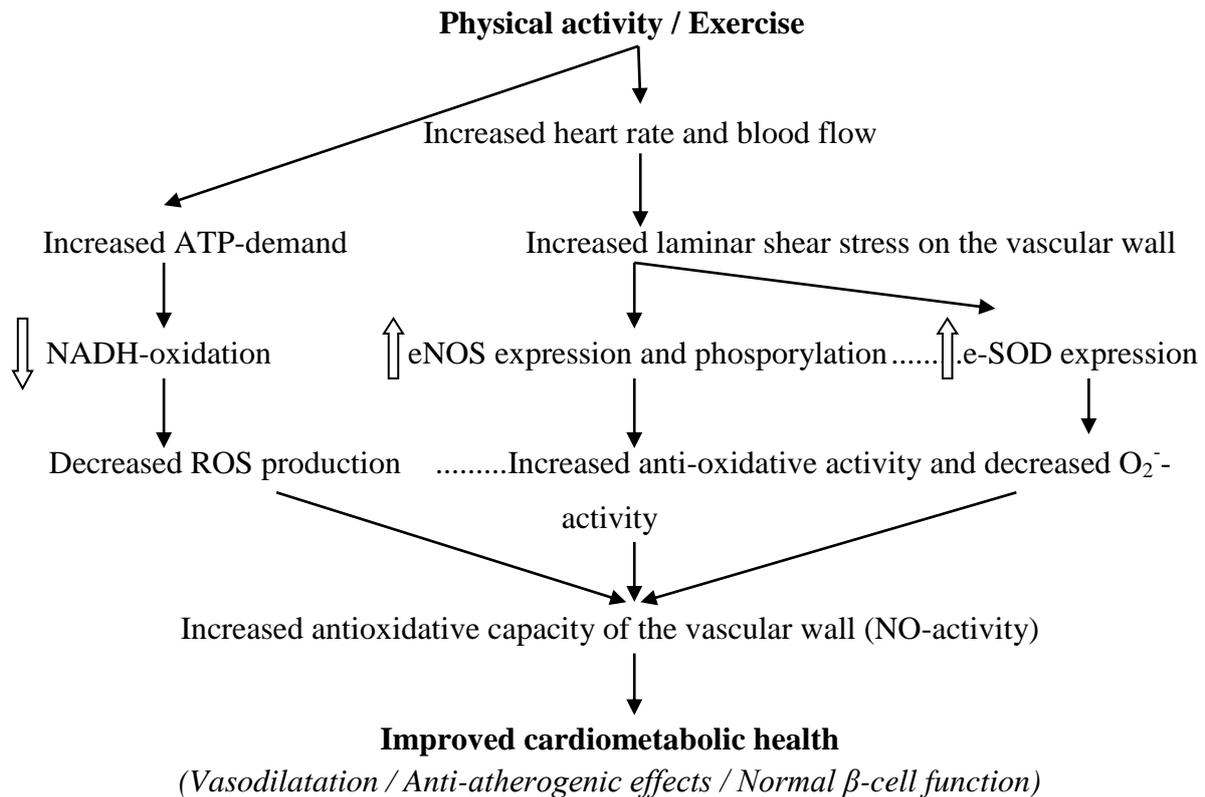


Figure 2.4: The anti-oxidative role of physical activity

2.5 CHRONIC STRESS AND TELOMERE BIOLOGY

Oxidative stress not only contributes to the development of disease, but is a major cause of ageing and age-related diseases (Epel, 2009:18). A frequently used biomarker for measuring the impact of ageing and to determine cardiovascular health is telomere length (Houben *et al.*, 2008:243). Chromosomal ends are protected by telomeres (DNA-protein complexes), preventing them from being recognized as double-strand breaks and to protect them from end-to-end fusion and degradation – thereby creating chromosomal stability (Epel *et al.*, 2004:17312). Telomere lengths vary considerably between different tissues and the length decreases with 20-200 base pairs with each cell division (Houben *et al.*, 2008:236) – newborns present with approximately 8 000 to 13 000 base pairs.

Ludlow and Roth (2011:8) indicated that research concerning telomere length in humans to date has mainly focused on samples from leukocytes (specifically peripheral blood mononuclear cells, PBMC), as these cells are easily obtained via simple isolated procedures

after venepuncture and also because this cell type is active during the disease process as they are immune cells. These authors suggested that future research should improve by studying tissue- and cell-specific telomere biology. However, Houben *et al.* (2008:237) indicated that despite tissue variability in telomere length, the rate of telomere shortening is approximately the same in the different tissues. Therefore, the telomere length of easily accessible tissue such as leukocytes cells could be assessed as surrogate for tissues involved in the systemic effects of chronic diseases.

Human telomere length is dynamic and telomeres shorten with each cell division / DNA-replication (Houben *et al.*, 2008:236; Zglinicki, 2002:339). Telomeres are not fully replicated with each cell division as the DNA polymerase enzyme cannot fully copy the end of the DNA strand – thus a region of the telomere is left uncopied, resulting in a shorter telomere with each cell division and cell senescence is triggered at crucial lengths (Epel *et al.*, 2004:17312; Houben *et al.*, 2008:236; Ludlow & Roth, 2011:2). For this reason telomere length can serve as a biomarker of a cell's biological age in humans (Epel *et al.*, 2004:17312).

Behavioural factors such as physical inactivity and smoking have previously been linked to telomere shortening (Cherkas *et al.*, 2008:157; Needham, 2013:6). Faster telomere shortening has been observed in cells with higher ROS levels and Zglinicki (2002:341) stated that telomere loss caused by oxidative damage is far greater than contributions from the end-replication problem alone. Immune cell telomere shortening (i.e. leukocyte cells) has been linked to many chronic diseases and early mortality (Armanios, 2013:1001; Epel, 2009:7; Weischer *et al.*, 2012:828).

The high energy intake and low energy expenditure phenomenon of modern society are not the only causes of increased oxidative stress. Epel and co-workers (2004:17312) found a significant association between current perceived as well as chronic psychological stress and higher oxidative stress, lower telomerase activity and shorter telomeres. Psychosocial stress has the potential to contribute to the increased oxidative stress burden by chronic activation of the autonomic and neuroendocrine stress response systems (Epel *et al.*, 2004:17314). In the event of a stressor, the brain responds by releasing chemical mediators, e.g. glucocorticoids or catecholamines that increase heart rate and blood pressure for the “fight or flight” response. In other words, allostasis achieves homeostasis by means of the

neuroendocrine responses of the hypothalamic-pituitary-adrenal (HPA) axis, as well as the sympathetic nervous system (SNS) (McEwen, 2008:176; Tsatsoulis & Fountoulakis, 2006:197).

In the case of psychological stress, however, this increased metabolic energy is not used physically for “fight-or-flight” and are restored in the body, leading to glucocorticoid and catecholamine excess. Allostatic overload occurs and the autonomic nervous system and hypothalamic-pituitary-adrenal axis responses are not “turned off” and the secretory end product of the HPA-axis, cortisol, remains high. Continues wear and tear of the cardiovascular system takes place, consequently resulting in; insulin resistance, visceral obesity, dyslipidemia, hypertension and left ventricle hypertrophy (Björntorp, 2001:73). However, a number of studies also suggest that the adrenal gland is hypoactive in some stress-related states and due to down-regulation of the cortisol receptors, hypocortisolism in chronic stress may occur (Fries *et al.*, 2005:1011; Heim *et al.*, 2000:2). Apart from a relationship between shorter telomeres and greater cortisol reactivity to an acute stressor and less cortisol inhibition during sleep, Tomiyana and colleagues (2012:44) also found a flatter diurnal cortisol slope was related to shorter telomeres. Hellhammer *et al.* (2004:11) found that although hypocortisolemic subjects scored high on measures of depression, perceived stress and physical complaints, they did not show allostatic load. This indicates that a hypocortisolemic stress response may have a protective role on cardiovascular and metabolic disorders (Hellhammer *et al.*, 2004:8).

The National Institute of Environmental Health Sister Study in the USA indicated that the effects of perceived stress on telomere length are dependent on neuroendocrine responsiveness and exposure to environmental stressors and that the dose-response for perceived stress and telomere shortening are stronger in older women (Parks *et al.*, 2009:559). Although urinary stress hormones alone did not show any relation to telomere shortening in this study, trends towards shorter telomeres were observed with higher and lower urinary cortisol levels (Parks *et al.*, 2009:555). Shorter telomeres were observed in women aged 35 to 74 (after adjusted for BMI, non-White race and smoking) with higher perceived stress and higher urinary epinephrine levels. Norepinephrine and dopamine did not show significant interactions with telomere length, however, a clear gradient with shorter telomere lengths across increased perceived stress categories were observed. Women in the moderate and high perceived stress categories with low cortisol levels showed non-

significantly shorter telomere lengths (Parks *et al.*, 2009:557). Figure 2.5 (adapted from Epel 2009:8) graphically demonstrates how chronic perceived stress results in biochemical imbalances due to direct central effects, as well as indirect effects for adiposity, eventually promoting leukocyte cellular aging.

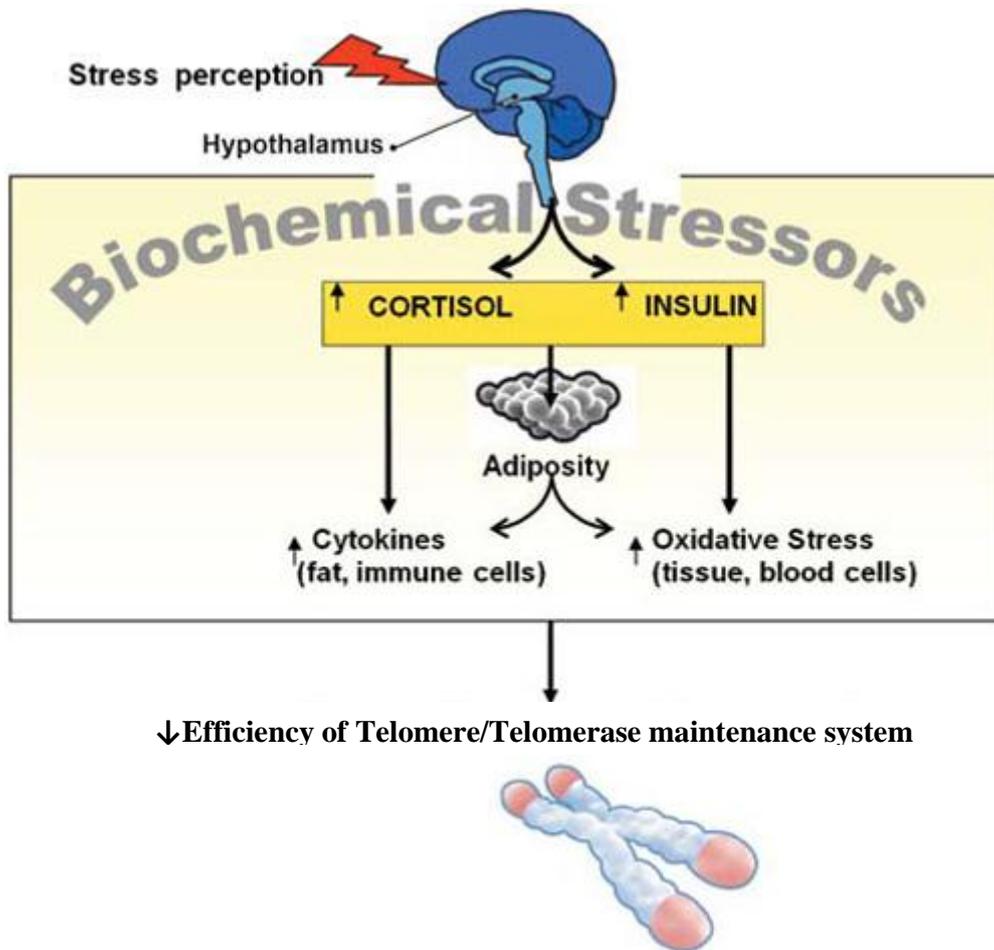


Figure 2.5: The link between chronic stress and cellular aging

Evidence suggesting a physical active lifestyle to have a buffering potential on the detrimental effects of chronic stress does exist (Cherkas *et al.*, 2008:155; Elosua *et al.*, 2003:327; Puterman *et al.*, 2010:10837) – (probable biological mechanisms explained in page 21 of this chapter). In a study on healthy post-menopausal women, higher perceived psychological stress levels were significantly associated with shorter telomere lengths (Puterman *et al.*, 2010:10840). However, above approximately 40 minutes of vigorous activity (defined by increased heart rate and sweating) over a three-day period, stress was no longer associated with shorter telomere lengths. Sixteen weeks of aerobic training in healthy

sedentary men and women showed a 15.9% decrease in oxidized LDL-concentrations (low-density lipoprotein), a contributing factor in the process of atherosclerosis (Elosua *et al.*, 2003:330). In this study a small sample of young men and women with an average age of 19.5 years, performed four sessions of 30 minutes per week at an intensity of 65-80% of an individual's VO²-max; that was progressed to five sessions of 50 minutes per week for the last eight weeks (Elosua *et al.*, 2003:328).

Cherkas *et al.* (2008:157) found a significant positive association between increased leisure time PA and leukocyte telomere lengths in Caucasian individuals – even after being adjusted for covariates such as age, sex, BMI, smoking, socio-economic status and physical activity at work. These findings were confirmed by a sample of 67 sets of twin that showed the leukocyte telomere length of the more active twin was on average longer than the less active twin (Cherkas *et al.*, 2008:155) – evidence that reduces genetic effects. The telomere lengths of individuals participating in leisure time PA for 199 minutes and more per week were the same as sedentary individuals (participating in sixteen minutes or less leisure time physical activity per week) ten years younger (Cherkas *et al.*, 2008:156). These findings suggest active individuals to be ten years younger than their inactive peers (Cherkas *et al.*, 2008:156).

Although the above-mentioned studies link PA to improved neuroendocrine function and telomere biology, controversy exists regarding the dose and type of PA associated with a positive response. As mentioned earlier, the updated PA guidelines suggest moderate physical activity for maintenance of health in adults aged 18 to 65 years (Haskell *et al.*, 2007:1803). However, literature, as seen above, indicates vigorous activity to have many beneficial effects. One of the reasons for the controversial results could be the lack of standardized measures of PA levels across studies, as well as the difference in PA level categorization. Although many valid measures exist, none of the above-mentioned studies used the same measurement tool to measure PA level (mostly self-report questionnaires were used) and all of the studies defined being physically active and being sedentary, differently. The positive results in the Puterman and colleagues study prompt these authors to conclude that it is reasonable to strongly advise and prescribe exercise to individuals reporting high levels of psychological stress (Puterman *et al.*, 2010:e10840). In my opinion, results of evidence-based research can only be trusted for implementation in practice if consistency in methodology, as well as outcome occurs across literature, is achieved, which is not currently the case.

2.6 SUMMARY

The proportion of YLL (a measure of premature mortality) due to NCDs has increased globally from 38% in the year 2000, to 47% in 2012 (WHO, 2014:46). Projections for the leading causes of death by 2030 for middle-income countries (such as South Africa) indicate that ischemic heart disease and contributors to non-communicable diseases (NCDs) will become greater mortality risks than HIV and AIDS (WHO, 2011^a:11). Cardiovascular diseases (CVD) contribute to almost half of the global NCD mortalities (WHO 2011^a:9), with high blood pressure shown as the leading risk factor and physical inactivity as one of the major modifiable behavioural risk factors (WHO, 2011^a:16, 19). More than 40% of South African adults are hypertensive and this country also has one of the highest physical inactivity rates worldwide (WHO, 2011^b:176).

The alarming summary of global and South African health statistics cannot but urge researchers to unite with health departments and policy-makers in the South African community to identify the burdens that affect a healthy lifestyle and develop health guidelines, which include practical and cultural specific recommendations to modify behavioural risk factors, such as being physically inactive. Matheson *et al.* (2011:1276) commented that the disparity between scientific knowledge regarding chronic diseases and practical implementation of preventative approaches is one of the most urgent concerns of healthcare providers worldwide. These authors urged the international sports and exercise community to take leadership and provide a new profession which dedicates the majority of its efforts to the prevention and management of chronic lifestyle-related diseases. Prevention by means of scientifically-based exercise programmes is one of the major focus points of the Biokinetics profession. However, these professionals currently only serve the financially privileged section of the population. Is it not time for Biokinetics to become part of the public health sector to implement cost-effective and culturally-specific PA health-promotion interventions?

To alter the alarming disease predictions, initiatives aimed, for example, at increasing PA in populations, rely on PA measures to implement interventions and monitor the effectiveness. In a review of methodologies used to measure PA, Warren and colleagues clearly stated that validity results of questionnaires assessed in one population cannot be systematically extrapolated to other populations, ethnic groups or other geographical regions (Warren *et al.*,

2010^b:131). The correct assessment of sedentary behaviour, as well as time spent doing activities of light intensity (occupational activities, active transport, household chores) is also limited by the use of questionnaires. Researchers in South Africa have mainly relied on PA questionnaires due to cost-effectiveness, regardless of evidence indicating that cultural perceptions and education levels alter the reliability of questionnaires.

For health-care professionals to educate patients in behaviour modification for better health and implement credible preventative strategies, research needs to eliminate the bias regarding self-report questionnaires by using technologically advanced objective measures – especially in the cultural, ethnical and geographical diverse South African setting. Currently we assume that one set of PA guidelines, derived from research on mainly the Caucasian population of the first world countries, using PA questionnaires, is applicable to all ethnic and culture groups globally. Maybe education initiatives for healthy living would be more trustworthy and adherence to health intervention programmes better if communities were to see that their specific needs are being considered. Better intervention strategies could be implemented from research if objective measures of both PA and cardiovascular and metabolic disease risk markers are used to accurately determine the PA dose-response relations in different ethnic groups.

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CHAPTER 3

The association between seven-day objectively measured habitual physical activity and ambulatory blood pressure: the SABPA study

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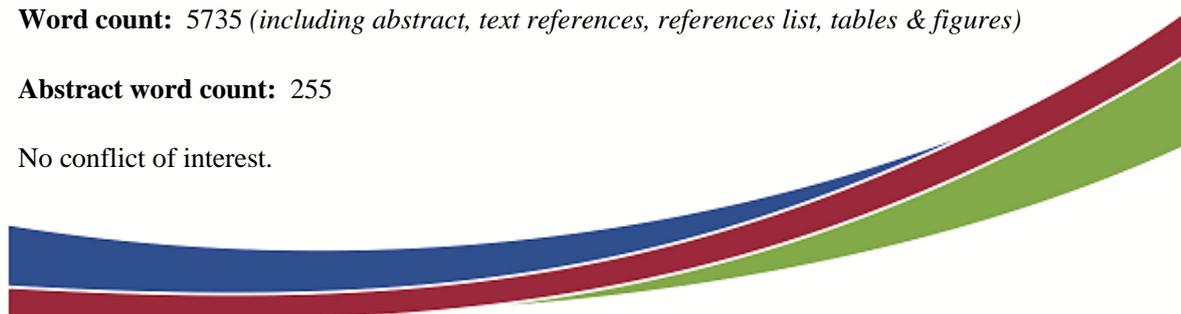
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ABSTRACT

Background: The dose-response relationship between physical activity intensity and blood pressure levels has primarily been obtained from self-reported questionnaires which have a limited ability to determine daily sedentary and light activity time. **Objectives:** To assess the association of 7-day objectively measured habitual physical activity with ambulatory blood pressure. **Methods:** Data of a subsample of the Sympathetic Activity and Blood Pressure in Africans prospective cohort study of African and Caucasian school teachers (n=134) were analysed. Seven-day habitual physical activity was assessed using the Actiheart device for associations with 24-h ambulatory blood pressure. All other lifestyle behaviours were objectively measured and anthropometric characteristics obtained. **Results:** The hypertensive groups spent significantly more awake time sedentary (p=0.004), as well as doing moderate- (p=0.020) and vigorous (p=0.025) intensity activities. Irrespective of race and sex, 24-h systolic and diastolic blood pressure, were respectively associated with daily awake sedentary time [$\beta=0.17$ (0.03, 0.31), p=0.018 and $\beta=0.18$ (0.03, 0.33), p=0.020], light activity time [$\beta=-0.15$ (-0.30, -0.01), p=0.043 and $\beta=-0.16$ (-0.32, -0.01), p=0.041], waist circumference [$\beta=0.45$ (0.30, 0.60), p \leq 0.000 and $\beta=0.32$ (0.17, 0.48), p \leq 0.000] and log gamma glutamyl transferase [$\beta=0.18$ (0.03, 0.34), p=0.018 and $\beta=0.24$ (0.08, 0.40), p=0.004]. Daily awake sedentary time showed the highest significance as predictor for hypertension of all four metabolic equivalent of task categories (Odds ratio=1.00, p=0.006). **Conclusion:** Spending more daily awake time sedentarily and less time doing light intensity activities, as well as a higher waist circumference and alcohol use had a negative influence on the ambulatory blood pressure of the African and Caucasian teachers in this study.

Key words: *physical activity, accelerometry measures, Actiheart, blood pressure, hypertension, ethnic differences*

3.1 INTRODUCTION

Hypertension was shown to be the most frequent risk factor for cardiovascular disease (CVD) in both rural and urban communities in sub-Saharan Africa with alarmingly low levels of awareness, treatment and control.¹ Projections in terms of the leading causes of death by 2030 for middle-income countries indicate that ischemic heart disease and contributors to non-communicable diseases (NCDs) will become greater mortality risks than HIV and AIDS.² Raised blood pressure (BP) was the greatest contributor to the global mortality rate, followed by tobacco use, raised blood glucose, physical inactivity, overweight and obesity.³ In South Africa, 39.9% of men and 34.9% of women aged 25 years and older suffer from high BP.⁴ An alarmingly high hypertension prevalence rate of 78% exists in South Africa for people aged 50 years and above. Only half of them are aware of their condition and a mere 14% receive treatment.⁵ South Africans also demonstrate high physical inactivity prevalence rates, with 46.4% and 55.7% of men and women, respectively not meeting the recommended physical activity (PA) guidelines.² It was previously indicated that physical inactivity predicts the likelihood of CVD beyond that of commonly measured cardiometabolic risk factors (cholesterol, glucose, BP and adiposity).⁶

The dose-response relationship between PA, risk of developing CVD and premature mortality are well documented, indicating a linear relationship of lower levels of risk with higher amounts of physical activity.^{7,8,9} However, Shimora and Lee stated that available data on the physical activity dose-response relation have primarily been obtained from observational studies using self-report questionnaires.¹⁰ Contemporary studies that employed objective assessment of habitual PA were able to examine light-intensity physical activity and sedentary behaviour during waking hours.^{11,12,13} Most research outcomes are, however, based on populations from North America, Australasia, and Europe,¹⁰ leaving a paucity of data from Africa.

The aim of the current study was to assess the association of habitual PA (expressed as time spent in different metabolic equivalent of task (MET) categories), objectively measured over a period of seven days, with ambulatory BP in African and Caucasian teachers living in the North West Province of South Africa. This study is unique in the sense that habitual PA was obtained from the total awake hours (± 17 hours per 24-h cycle) of a seven-day recording in all participants. All other lifestyle behaviours (smoking and alcohol consumption) were objectively measured and hypertension status was derived from the gold standard 24-h

ambulatory BP-measurement. Also, both the African and Caucasian participants were school teachers and are therefore more likely to be economically homogeneous.

3.2 METHODS

3.2.1 Design and subjects

This sub-study formed part of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study with a target population of urban African and Caucasian school teachers from the Dr Kenneth Kaunda Education District in the North West Province of South Africa. The North West Department of Education, as well as the South African Democratic Teachers' Union, granted permission for the study and ethical approval was obtained from the North-West University (NWU), South Africa (0003607S6). The SABPA study conforms to the principles outlined in the Declaration of Helsinki (revised 2004) and all participants signed informed consent prior to the start of data collection. The cohort profile of the SABPA study is well explained by Malan et al.¹⁴

Data collection commenced during February to May in 2011 (African teachers, n=173) and again during the same time frame in 2012 (Caucasian teachers, n=186), avoiding seasonal influences. Pregnant or lactating women, individuals who donated blood or had been vaccinated in the three-months prior the commencement of testing, as well as those with a tympanum temperature greater than 37.5°C were excluded from the SABPA study. The data of another 143 of the follow-up participants were disregarded in this sub-study, either because they did not comply with wearing the Actiheart-device for a full seven days or the Actiheart recordings indicated more than 40 minutes of daily non-contact time during awake hours. Furthermore, all HIV-positive participants and those using anti-hypertensive and/or anti-diabetic drugs (n=82) were excluded. The final participant sample for this sub-study comprised 134 (37%) teachers.

3.2.2 Data-collection procedure

Data were collected in four participants per weekday (February to May), with the clinical assessments performed over a two-day period. On day 1, at 07h00, a Cardiotens apparatus (24-h ambulatory BP measurement) was fitted to all participants at their schools. Participants then resumed their normal daily activities and were transported to the university at

approximately 15h00 for the clinical assessments. They were introduced to the experimental set-up to lessen anticipation stress.¹⁵ Participants stayed overnight in a well-controlled environment at the Metabolic Unit Research Facility of the NWU where they had a standardized dinner and were asked to refrain from taking any beverages after 22h00.

Participants were woken at 07h00 on day 2, the Cardiotens apparatus was disconnected and the anthropometric measurements commenced. Hereafter, participants rested in a semi-recumbent position for a resting 12-lead electrocardiography (ECG) followed by blood sampling one hour later. A resting blood sample of 65 ml was obtained by a registered nurse from the brachial vein branches of the dominant arm using a winged infusion set and immediately sent to the laboratory for storage. The participants then showered and the Actiheart device for the seven-day PA measurement was fitted. Each participant received four extra electrodes to ensure that the Actiheart was immediately refitted if it should become disconnected during the course of the seven days. Participants were instructed to carry on with their habitual daily activities wearing the monitor at all times whilst awake and asleep. The Actiheart was collected from each participant at the various schools on the eighth day and the data downloaded onto the computer for storage, viewing and analysis.

3.2.3 Measurements and equipment

Anthropometric measurements

Participants' height, weight and waist circumference were measured using the standardized methods of the International Society for Advancement of Kinanthropometry (ISAK).¹⁶ These measurements were used to calculate the body mass index (BMI, $\text{kg}\cdot\text{m}^{-2}$)¹⁷, the body surface area (BSA, m^2)¹⁸ and the waist-to-height-ratio (WHtR).¹⁹ Intra- and inter-observer variability was less than 10%.

Blood pressure and biochemical measurements

The Cardiotens apparatus (Meditech CE0120[®], Meditend, Hungary), a British Hypertension Society validated device, was used to obtain a 24-hour ambulatory BP-measurement (systolic blood pressure (SBP) and diastolic blood pressure (DBP)). Suitable cuff sizes were applied to the non-dominant arms and BP was measured at 30-min intervals during the day and 60-min intervals at night. Successful mean inflation rates for the ABPM period were 86%

($\pm 9.7\%$) in Africans and 94% ($\pm 6.0\%$) in Caucasians. Participants were asked to record any abnormalities such as visual disturbances, headache, nausea, fainting, palpitations, PA and emotional stress on their ambulatory diary cards. The data were analysed using the CardioVisions 1.15.2 Personal Edition software (Meditech[®]). Hypertension status was defined as ambulatory BP: SBP ≥ 130 and / or DBP ≥ 80 .²⁰

A sterile winged infusion set was used to obtain blood samples from the antebachial vein branches by a registered nurse and handled according to standardized procedures and stored at -80°C until analysis. Fasting serum samples were analysed for using the sequential multiple analyser computer (Konelab 20i; Thermo Scientific, Vantaa, Finland). Serum cotinine levels were determined with a homogeneous immunoassay (Automated Modular, Roche, Basel, Switzerland). HIV-status was measured using the First Response kit (Premier Medical Corporation, India) as well as the confirmatory Pareekshak test (Bhat Biotech, India).

Physical activity measurement

The weekly habitual PA of participants was measured over a period of seven consecutive days with an Actiheart (GB0/67703[®], CamNtech Ltd., Cambridgeshire, UK). After awakening at 07h00 on the second day, participants rested in the semi-recumbent position for 30 minutes after which the resting 12-lead electrocardiogram (NORAV Medical Ltd PC 1200, software version 5.030, Kiryat Bialik, Israel) was taken. The 12-lead ECG resting heart rate was used to calculate the sleep heart rate, required by the Actiheart programme when the device was fitted to each participant.

The seven-day recordings were visually inspected for each individual to distinguish between time awake (including sedentary hours), and time asleep for each 24-h (hour) cycle. The heart rate (HR) was considered along with the Metabolic Equivalent of Task (MET, 1 MET regarded as being asleep) and activity level to distinguish sleeping time from being awake. Where the HR in the evenings gradually dropped and the activity level was equal to zero, the participant was considered to be sleeping. The end of sleeping could clearly be seen by an immediate increase in the HR of more than 10 to 20 beats per minute relative to preceding sleeping HR, as well as an increased MET and activity level. The daily awake minutes were categorised according to daily awake sedentary time (≤ 1.5 METs), daily awake light activity time (> 1.5 & < 3 METs), daily awake moderate activity time (≥ 3 & < 6 METs) and daily

awake vigorous activity time (≥ 6 METs).²¹ For the remainder of this article, the MET-categories will only be expressed as sedentary time, light activity time, moderate activity time and vigorous activity time.

3.2.4 Statistical analyses

Statistical analyses were performed with the Statistica 12 (StatSoft Inc., 2014) programme. Departure from normality was evaluated using the Shapiro-Wilk test and Quantile-Quantile plots. The serum γ -GT was log-transformed and serum cotinine was categorized. Moderate and vigorous activity was not log-transformed as all residual plots of the multivariate regression analyses that included these two measures, indicated normal distribution. One-way analyses of covariance (ANCOVA) were used to determine significant differences between the lifestyle behaviours (habitual PA, smoking and alcohol use) and anthropometric characteristics of hypertensive and normotensive participants adjusting for age. Partial correlations (also adjusted for age) indicated the significant associations of the lifestyle- and anthropometric characteristics with ambulatory SBP and DBP, respectively. Forward stepwise regression analyses, as well as logistic regressions were performed in various models to assess associations between the dependent markers, ambulatory SBP and DBP adjusting for age, waist circumference and lifestyle behaviours (sedentary time, light-, moderate, vigorous activity time, serum cotinine and log serum γ -GT). The times spent in MET-categories were each separately entered into the models. Last, race- and sex-specific waist circumference cut points (African men ≥ 94 cm; African women ≥ 98 cm; Caucasian men ≥ 90 cm and Caucasian women ≥ 80 cm)²² were used to categorize participants above these cut-offs, along with hypertension status into three different groups – those with high waist circumferences and hypertension, those with either and lastly the participants with neither. Data were considered to be statistically significant for all the analyses at $p \leq 0.05$.

3.3 RESULTS

Table 3.1 displays the basic lifestyle, anthropometric and ambulatory blood pressure characteristics of the study population. The Africans comprised 43% (n=23) men and 57% (n=31) women, whereas the Caucasians were 40% (n=32) men and 60% (n=48) women. Of the 17 hours daily awake time (minutes in Table 1 divided by 60), the group on average spent 7.5 hours sedentary, 6.5 hours doing light, 2.9 hours doing moderate and less than 6 minutes

per day doing vigorous activities. The race and sex distribution of hypertensive participants (n=58) was as follows: African men = 31% (n=18), African women = 24% (n=14), Caucasian men = 26% (n=15) and Caucasian women = 19% (n=11). Keep in mind that none of these participants received anti-hypertensive drug treatment.

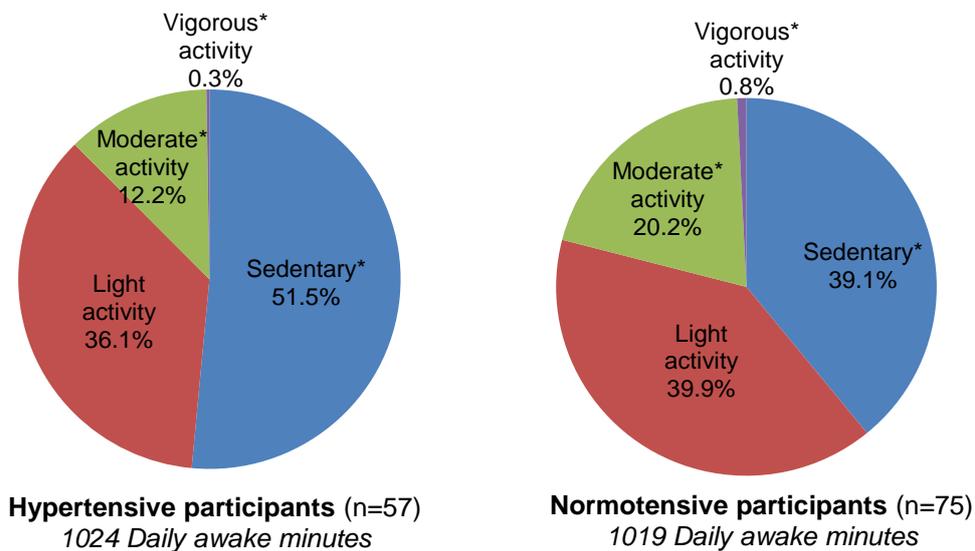
Table 3.1: Descriptive characteristics of the study population

| | Total population (N=134) |
|--|-------------------------------------|
| Africans, N (%) | 54 (40) |
| Caucasians, N (%) | 80 (60) |
| Anthropometric and lifestyle characteristics | |
| | Mean ± SD |
| Age (years) | 47.90±8.6 |
| BMI (kg/m ²) | 28.24±6.4 |
| Body surface area (m ²) | 1.94±0.3 |
| Waist circumference (cm) | 92.05±14.9 |
| Serum γ -GT (U/L) | 36.06±41.0 |
| Smoking, n (%) | 14 (10.5) |
| Daily awake time (minutes) | 1023.68±63.6 |
| Daily awake sedentary minutes, ≤ 1.5 METs | 450.87±246.8 |
| Daily awake light activity minutes, >1.5 & <3 METs | 392.09±171.9 |
| Daily awake moderate activity minutes, ≥ 3 & <6 METs | 175.00±191.8 |
| Daily awake vigorous activity minutes, ≥ 6 METs | 5.71±13.0 |
| Ambulatory blood pressure and physiological markers | |
| | Mean ± SD |
| 24-h SBP (mmHg) | 125±16.2 |
| 24-h DBP (mmHg) | 77±10.7 |
| MAP | 93±11.6 |
| Hypertensive (SBP ≥ 130 and / or DBP ≥ 80), n (%) | 58 (43.3) |
| Glycated haemoglobin (%) | 5.60±0.4 |
| Glycated haemoglobin above cut point ($>5.7\%$), n(%) | 42 (31.3) |
| C-Reactive protein (mg/L) | 3.24 ±4.8 |

γ -GT, Gamma Glutamyl Transferase; BMI, Body mass index ; METs, Metabolic Equivalent of Task; SBP, Systolic blood pressure; DBP,

Diastolic blood pressure and MAP, Mean arterial pressure

Evaluating the interactions of the different MET-categories on hypertension status, sedentary time ($F(1,123) = 6.7$; $p=0.011$), moderate activity time ($F(1,123) = 7.9$; $p=0.006$) and vigorous activity time ($F(1,123) = 7.5$; $p=0.007$) indicated significant interactions with hypertension. Figure 3.1 shows that hypertensive participants spent more than half of their daily awake time being sedentary (8.8 hours per day), which was significantly more than the normotensive participants ($p=0.004$) who on average spent 6.6 hours daily awake time sedentary. Light activity time was more-or-less the same in both groups, while the hypertensive participants spent significantly less time doing activities of moderate- ($p=0.020$) and vigorous ($p=0.025$) intensity. The vigorous intensity activities of both groups were however below 10 minutes per day.



* Statistically significant different ($p \leq 0.05$)

Figure 3.1: Percentage of daily awake time spent in the different MET-categories for hypertensive and normotensive participants

Additionally, Table 3.2 indicates that the average waist circumference of the hypertensive participants was almost 10 cm larger than the normotensive participants, and they also had significantly greater values for BMI, BSA and WHtR. Note how the WHtR is above the norm of 0.5 in both the normotensive and hypertensive groups. Hypertensive participants

also demonstrated significantly higher alcohol use (serum γ -GT) and a greater percentage of the hypertensive participants smoked.

Table 3.2: ANCOVAS indicating differences in risk factors between hypertensive and normotensive participants

| | Hypertensive (n=58) | Normotensive (n=76) | p-value |
|---|-------------------------------|-------------------------------|----------------|
| Variables, Mean (\pm95% CI) | | | |
| BMI (kg/m ²) | 29.84 (28.2, 31.5) | 27.02 (25.6, 28.5) | 0.011* |
| BSA(m ²) | 2.03 (2.0, 2.1) | 1.87 (1.8, 1.9) | \leq 0.001* |
| Waist circumference (cm) | 97.60 (93.9, 101.3) | 87.81 (84.6, 91.0) | \leq 0.001* |
| Waist/Height | 0.57 (0.6, 0.6) | 0.53 (0.5, 0.5) | 0.003* |
| Cotinine, n (%) | 10 (17.5) | 4 (5.3) | 0.024* |
| γ -GT (U/L) | 49.38 (39.1, 59.7) | 26.12 (17.2, 35.0) | 0.001* |

BMI, Body mass index; BSA, Body surface area; γ -GT, Gamma Glutamyl Transferase. Adjusted for age. * $P \leq 0.05$.

Partial correlations in the total group (adjusted for age and log γ -GT) indicated both the 24-h SBP and the 24-h DBP to have significant positive associations with BMI ($r=0.453$; $p \leq 0.000$ and $r=0.29$; $p=0.001$), BSA ($r=0.45$; $p \leq 0.000$ and $r=0.35$; $p \leq 0.000$), WC ($r=0.48$; $p \leq 0.000$ and $r=0.35$; $p \leq 0.000$), WHtR ($r=0.45$; $p \leq 0.000$ and $r=0.28$; $p=0.001$), sedentary time ($r=0.21$; $p=0.017$ and $r=0.21$; $p=0.015$) and a significantly negative association with light activity time ($r=-0.27$; $p=0.005$ and $r=-0.24$; $p=0.005$).

Race and sex did not indicate any significance in terms of either ambulatory SBP or DBP in multiple regressions analyses adjusted for race, sex, age, waist circumference, and lifestyle behaviours (sedentary time, light-, moderate-, vigorous activity time, smoking and log γ -GT). Race and sex were therefore excluded as covariate for the models used in table 3.3 due to the small sample size of this study. BMI, BSA and WHtR were also not included due to the strong collinearity of these variables with WC, which indicated the highest correlation with MAP ($r=0.416$, $p \leq 0.001$). Time spent in different MET-categories was added separately into each model. Irrespective of race and sex, waist circumference and log γ -GT indicated significant positive associations with both 24-h SBP and DBP in all four models (Table 3.3). Only sedentary and light activity time showed significant associations of the four MET-

categories - respectively indicating significant positive and negative associations with ambulatory blood pressure.

Table 3.3: Forward stepwise regression analyses results examining the relationship between anthropometric and lifestyle characteristics with 24-h ambulatory blood pressure

| | 24-h SBP | 24-h DBP |
|-------------------------------|--------------------------------------|--------------------------------------|
| | (N=134) | (N=134) |
| | B (±95% CI) | B (±95% CI) |
| Model 1: | <i>Adjusted R² = 0.37</i> | <i>Adjusted R² = 0.27</i> |
| Waist circumference (cm) | 0.45 (0.30, 0.60)** | 0.32 (0.17, 0.48)** |
| Log γ -GT | 0.18 (0.03, 0.34)** | 0.24 (0.08, 0.40)* |
| Sedentary time (minutes) | 0.17 (0.03, 0.31)* | 0.18 (0.03, 0.33)* |
| Model 2: | <i>Adjusted R² = 0.36</i> | <i>Adjusted R² = 0.27</i> |
| Waist circumference (cm) | 0.42 (0.27, 0.57)** | 0.30 (0.13, 0.47)** |
| Log γ -GT | 0.20 (0.05, 0.35)** | 0.26 (0.30, 0.42)* |
| Light activity time (minutes) | -0.15 (-0.30, -0.01)* | -0.16 (-0.32, -0.01)* |
| Model 3: | <i>Adjusted R² = 0.35</i> | <i>Adjusted R² = 0.26</i> |
| Waist circumference (cm) | 0.49 (0.34, 0.64)** | 0.36 (0.20, 0.52)** |
| Log γ -GT | 0.20 (0.05, 0.35)* | 0.25 (0.09, 0.42)* |
| Model 4: | <i>Adjusted R² = 0.34</i> | <i>Adjusted R² = 0.25</i> |
| Waist circumference (cm) | 0.48 (0.33, 0.63)** | 0.36 (0.20, 0.52)** |
| Log γ -GT | 0.21 (0.06, 0.36) | 0.27 (0.11, 0.43)* |

B denotes standardized regression coefficient. *p≤0.05; ** p≤0.001. Additional covariates considered for models: Model 1: Age, serum cotinine; Model 2: Age, serum cotinine; Model 3: Age, serum cotinine, moderate activity time; Model 4: Age, serum cotinine, vigorous activity time.

Logistic regression analyses (Table 3.4) were performed to assess the likelihood of age, waist, smoking, log γ -GT and the time spent in the four MET-categories to predict hypertension. The time spent in different MET-categories was again separately entered into each model. The different models explained between 17% and 29% of the variance in hypertension-status. Waist circumference was significantly associated with hypertension in all four models. Time spent doing activities of light intensity, was the only MET-category

not indicating any significance as predictor for hypertension, which is contradictory to both the partial correlations and multivariate regression results.

Table 3.4: Logistic regression analyses indicating significant predictors for hypertension

| Predictor | Odds ratio ($\pm 95\%$ CI) | P-value |
|---|-----------------------------|---------|
| Model 1: (Cox-Snell $R^2 = 0.22$; Nagelkerke $R^2 = 0.29$) | | |
| Waist circumference (cm) | 1.04 (1.01, 1.07) | 0.028 |
| Sedentary time (minutes) | 1.00 (1.00, 1.00) | 0.006 |
| Model 2: (Cox-Snell $R^2 = 0.17$; Nagelkerke $R^2 = 0.23$) | | |
| Waist circumference (cm) | 1.03 (1.00, 1.07) | 0.035 |
| Log γ -GT | 3.59 (2.51, 4.67) | 0.021 |
| Model 3: (Cox-Snell $R^2 = 0.22$; Nagelkerke $R^2 = 0.29$) | | |
| Waist circumference (cm) | 1.05 (1.02, 1.08) | 0.005 |
| Log γ -GT | 3.06 (1.98, 4.13) | 0.041 |
| Moderate activity time (minutes) | 1.00 (1.00, 1.00) | 0.008 |
| Model 4: (Cox-Snell $R^2 = 0.22$; Nagelkerke $R^2 = 0.29$) | | |
| Waist circumference (cm) | 1.05 (1.02, 1.08) | 0.005 |
| Log γ -GT | 3.75 (2.65, 4.85) | 0.018 |
| Vigorous activity time (minutes) | 0.94 (0.89, 1.00) | 0.030 |

Statistical significance were set at $P \leq 0.05$. γ -GT, Gamma Glutamyl Transferase. Covariates considered for in models: Model 1: Age, waist, smoking, log γ -GT and sedentary time; Model 2: Age, waist, smoking, log γ -GT and light activity time; Model 3: Age, waist, smoking, log γ -GT and moderate activity time; Model 4: Age, waist, smoking, log γ -GT and vigorous activity time.

All the analyses indicated strong associations between waist circumference and ambulatory BP. Therefore, acknowledging sex and ethnic differences, race- and sex-specific waist circumference cut-offs were used along with hypertension to categorise the populations (Figure 3.2) into those with waist circumferences above the cut-point along with hypertension, those with either a high waist circumference or hypertension and thirdly, those with neither (apparently healthy).²²

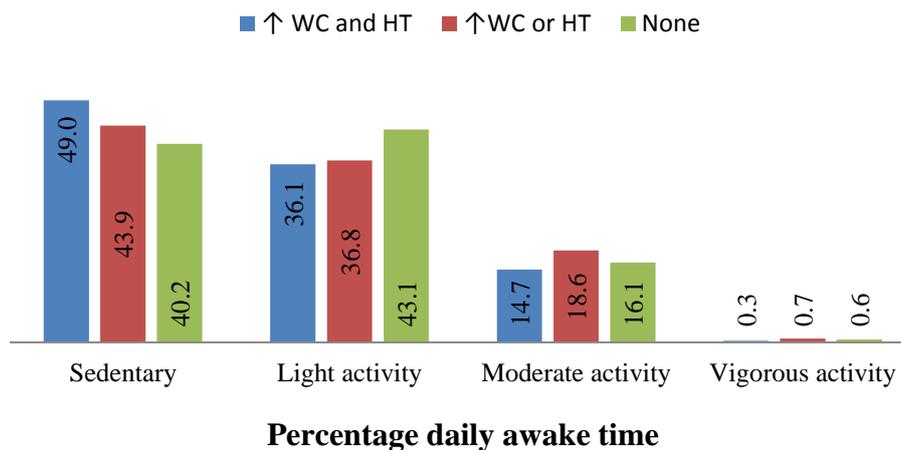


Figure 3.2: ANCOVAS (adjusted for age and log γ -GT) indicating the difference in percentage of daily awake time spent in different MET-categories between: 1) hypertension (HT) **AND** a high waist circumference (WC); 2) hypertension **OR** a high waist circumference; 3) **None** (apparently healthy)

Although not significant, Figure 3.2 clearly shows that the participants with a high waist circumference and hypertension spent more daily awake time sedentary and less time in all three activity categories than the other two groups. The apparently healthy participants had the greatest percentage of light activity time (which showed a significant negative correlation with waist circumference; $r=0.23$, $p=0.010$) and the least sedentary time).

3.4 DISCUSSION

The African and Caucasian teachers in this study who spent more awake time sedentary and less time doing light activities had significantly higher ambulatory SBP and DBP. This is in line with the research of Gando and co-workers who found that arterial stiffness was negatively associated with time spent in light PA in unfit older adults.²³ Using the Actiheart (a combined heart rate and accelerometer device)²⁴ to measure habitual PA ensured energy expenditure of all intensities, and sedentary time was included for association with ambulatory BP. Also, the habitual PA measures were obtained during total awake time (just over 17-hours), which is substantially more than previous studies using objective devices to

measure habitual PA.^{25,26} The occupation of our study population could also have contributed to the high amount of sedentary and light activity time, as standing (1.8-3METs), slow walking (2.5 METs) and sitting while working (1.5-2 METs), forms a great part of a teacher's day (each listed as sedentary or light energy cost activities).²⁷ Furthermore, many of the teachers were involved in coaching and refereeing for different sports codes, which could explain the high average moderate activity time.

Sedentary time showed itself to be a slightly better predictor of hypertension than moderate and vigorous activity time. Compared to normotensive participants, the hypertensive participants in this study spent 12% more of their daily awake time sedentary. Bauman and colleagues called for sedentary behaviours (watching television and working on a computer) and incidental energy expenditure (using the stairs instead of elevator) to be considered in the description of PA recommendations.²⁸ In the 1900s, the research of Morris and Crawford already reported that men doing sedentary jobs had more and more severe coronary artery disease (CAD) during middle-age than those with physically active jobs.²⁹ Since then, many studies have indicated associations between sedentary time and cardiovascular-, as well as cardiometabolic disease.^{30,31,32,33}

The dose and the type of PA for health benefits remain inconsistent in the literature. Although moderate and vigorous activity was significant as predictor for hypertension in the current study, the partial correlations and regression analysis did not indicate such an association with ambulatory blood pressure. A large prospective cohort focussing on PA dose-response relationship showed a reverse J-shaped relation, with higher major- and non-fatal cardiovascular events, as well as higher cardiovascular and all-cause mortality rates in the subjects who never or rarely participated in PA, as well as in those with daily or five to six times per week participation in PA.³⁴ A meta-analysis of prospective cohort studies on the effect of PA on hypertension risk suggested an inverse dose-response association between recreational PA and risk of hypertension, whereas no such association was observed for occupational PA.³⁵

Apart from the PA measures, waist circumference and log γ -GT were the only variables that consistently remained associated with both ambulatory SBP and DBP in all the regression models and was also more significant predictors of hypertension. This is consistent with Schutte and colleagues, who found that elevated γ -glutamyl transferase levels and abdominal

obesity were the strongest contributors in the development of hypertension.³⁶ Measures of abdominal obesity (WHtR and waist circumference) were previously found to correlate better with arterial stiffness and subclinical atherosclerosis than measures of general obesity (BMI and body fat percentage).³⁷ Contradictory to the meta-analysis results of Ashwell and colleagues,¹⁹ waist circumference and even BSA showed stronger associations with ambulatory BP than WHtR in the present study population, with more daily light intensity activities being related to lower waist circumferences. Teachers with both a high waist circumference and hypertension also spent the least time of all in physical activity MET-categories, as well as the most time being sedentary (although not significant). Actigraph accelerometry measurements over a period of seven days found breaks in prolonged sedentary time to be beneficial for waist circumference.³¹ This, along with the results of the current study supports the suggestion that public health strategies should give greater attention to lifestyle behaviours.^{38,39,36}

In conclusion, the results of the present study showed that less daily awake sedentary and more light-intensity activity time, as well as a waist circumference below the race and sex specific cut-off points and lower alcohol use were beneficial to both the 24-h ambulatory SBP and DBP. The strongest predictors for hypertension in these African and Caucasian teachers were higher log serum γ -GT, a greater waist circumference and sedentary time. Although this study provides valuable information, it is not without limitations. The study is cross-sectional, thus we cannot infer causal links from the data. The sample size was relatively small, essentially due to the exclusion of the participants who did not comply with the instructions for wearing the Actiheart device. This may have affected the statistical power for uncovering some significant associations. Individual calibrations (step testing) prior to fitting the Actiheart devices were not performed in this study due to the high clinical CVD risk of many participants,⁴⁰ thus self-reported PA was used instead to choose a PA level on the Actiheart programme.

3.5 PERSPECTIVES

This study highlighted the detrimental effect of sedentary time on health. More important, though, was that the recording of habitual PA during total awake hours emphasized the true protective potential of longer daily light-intensity activity time on blood pressure. These

results strengthen the suggestion of Bauman and colleagues to add sedentary behaviour, as well as light intensity activities of daily living to the current PA guidelines for health promotion. This is, however, only possible if future studies record objective PA measures during total awake time, as in the present study. Researchers are also urged to define daily activity energy expenditure according to time spent in the different MET-categories, as this would help health promotion practitioners to use the *Compendium of physical activities* of Ainsworth and colleagues when educating patients on breaking sedentary time with for instance light intensity activities. Maybe people would be more amenable to small changes rather than complying with the moderate and vigorous PA recommendations.

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3.7 DISCLOSURES

None.

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CHAPTER 4

The association between objectively measured physical activity, chronic stress and leukocyte telomere length: the SABPA study

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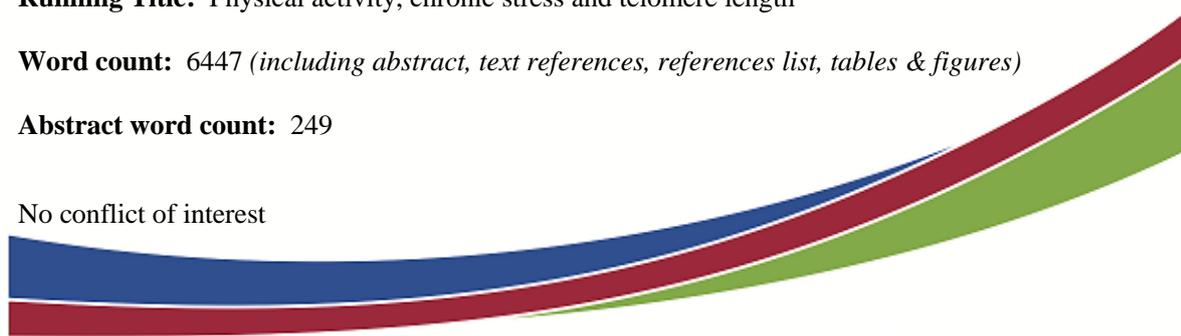
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ABSTRACT

Physical activity buffers chronic stress and age-related and cardiovascular disease risks, thereby potentially slowing telomere shortening. This study aimed to determine the association between seven-day objectively measured habitual physical activity (PA), chronic stress and leukocyte telomere length. Excluding HIV⁺-participants, the data of African (n=96) and Caucasian (n=107) school teachers of the Sympathetic activity and Ambulatory Blood Pressure in Africans study were analysed. All lifestyle characteristics (including PA) were objectively measured, whereas the general health questionnaire and serum cortisol levels indicated cognitive and chronic distress. Leukocyte telomere lengths were measured using the quantitative real-time polymerase chain reaction. Africans presented with a mean hypertension state and had significantly shorter telomeres ($p \leq 0.000$) and higher cognitive distress scores ($p = 0.001$) than Caucasians, with no differences in cortisol levels. An older age [$\beta = -0.28$ (-0.40, -0.16), $p \leq 0.000$], higher alcohol consumption [$\beta = -0.21$ (-0.36, -0.08), $p = 0.003$] and increased central obesity [$\beta = -0.17$ (-0.30, -0.03), $p = 0.017$] were associated with shorter telomeres. Time spent in the different PA metabolic equivalent of task categories was not associated with either cortisol or telomere length. However, a sensitivity analysis showed that light intensity activity time significantly correlated with lower waist circumferences ($r = -0.21$, $p = 0.004$); a parameter associated with both cortisol [$\beta = -0.24$ (-0.41, -0.09), $p = 0.005$] and telomere length [$\beta = -0.17$ (-0.30, -0.03), $p = 0.017$]. We conclude that habitual physical activity, expressed as time spent in different MET-categories, was not directly associated with markers of chronic stress or telomere length. However, increasing light intensity PA could lower age-related disease risk by contributing the maintenance of a healthy waist circumference.

Key words: *physical activity, exercise, chronic stress, perceived stress, age-related disease, telomere shortening*

4.1 INTRODUCTION

There is extensive evidence to demonstrate that lifestyle modifications, such as sufficient amounts of physical activity (PA) and a healthy diet, enhance quality of life, contribute to cardiometabolic disease prevention and longevity [1, 2]. Unhealthy behaviours, such as physical inactivity, poor dietary intake, alcohol abuse and smoking contribute to a number of disease processes, such as oxidative stress and low grade inflammation which increases the risk of morbidity and mortality [3]. During long-term psychological stress the increased metabolic energy normally used physically for “fight-or-flight” responses is restored in the body, leading to glucocorticoid and catecholamine excess. Therefore, allostatic overload occurs in chronic stress states, as the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis responses are not “turned off” and the secretory end product of the HPA-axis, cortisol, remains high [4]. These heightened stress hormone secretion, such as cortisol and insulin, increase oxidative stress, thereby contributing to ageing and age-related diseases [3]. Increased oxidative stress interferes for instance with the protective role of nitric oxide (NO) which functions as an antioxidant, vasodilator, antiplatelet component and anti-adhesive component if produced in vascular endothelial cells [5]. An increasingly used biomarker for measuring the impact of ageing and to determine cardiovascular health is telomere length [6]. Epel and colleagues, for instance, found that short telomeres and telomerase activity were significantly related to high levels of cortisol, epinephrine and norepinephrine; and that low telomerase activity was associated with several CVD risk factors [7].

Telomeres are DNA-protein complexes that protect chromosomal ends and shorten with each cell division, triggering cell senescence at crucial lengths [6, 8]. Possible mechanisms for telomere shortening are multifactorial and include current perceived stress, chronic psychological stress (in other words, the pathways of stress-related hormones), oxidative stress and inflammation [8, 9]. The National Institute of Environmental Health Sister Study in the USA indicated that the effects of perceived stress on telomere length are dependent on neuroendocrine responsiveness and exposure to environmental stressors [10]. Research suggests that a physically active lifestyle can buffer the detrimental effects of chronic stress [11, 12]. Puterman and colleagues [13] even recommended prescribing exercise to individuals reporting high levels of psychological stress. In their review of PA and telomere

biology, Ludlow and Roth concluded that PA improves cellular conditions and therefore has the potential to reduce age-related disease risk through impacts on telomere biology [9].

A limitation of previous research lies in the assessment of physical activity, which has often been self-reported and thus unable to accurately estimate PA in all metabolic equivalent of task (MET) categories. Therefore, the current study aimed to determine the association between 7-day objectively measured habitual PA, cognitive and chronic distress and leukocyte telomere length in a cohort of Africans and Caucasians.

4.2 METHODS

4.2.1 Design and participants

The follow-up data of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study, collected from February to May 2011 and 2012, respectively, were used for the purpose of this sub-study. Permission for the study was obtained from the North West Department of Education, as well as the South African Democratic Teachers Union and all participants signed informed consent. The SABPA study conforms to the principles outlined in the Declaration of Helsinki (revised 2004) and abided by the institutional guidelines and was approved by the Ethics Committee of the North-West University, South Africa (0003607A6). The cohort profile of the SABPA study is described elsewhere [14].

A cohort of urban African (n=173) and Caucasian (n=186) school teachers were recruited from the Dr Kenneth Kaunda Education District in the North West Province of South Africa. Pregnant or lactating women, individuals who donated blood or have been vaccinated in the three months prior the commencement of testing and those with a tympanum temperature greater than 37.5°C have been excluded prior to commencement of testing. Only 216 of the follow-up participants complied with wearing the Actiheart for a full seven days and with less than 40 minutes of total daily interruption periods. Colley *et al.* stated that allowable interruption periods (lost- and non-wear time), when using accelerometry to measure PA, are inconsistent in literature [15]. After close inspection of the current study's raw Actiheart data, an interruption period of no more than 40 minutes awake time per day was chosen to ensure habitual PA data as close to a full seven days as possible was obtained. Further, all

HIV-positive participants (n=13) were excluded as the average telomere lengths of these individuals differed significantly from the group average - leaving a final analytic sample of 203 (Africans, n=96 and Caucasians, n=107).

4.2.2 Measurements and equipment

Blood pressure

The Cardiotens apparatus (Meditech CE0120[®], Meditend, Hungary), a validated British Hypertension Society device, was used to obtain the 24-hour ambulatory blood pressure measurement (ABPM) from the non-dominant arm using suitable cuff sizes. Measures were obtained every 30 minutes during the day and set at 60-min intervals at night. Successful mean inflation rates for the ABPM period were 85.29% ($\pm 9.35\%$) in Africans and 93.62% ($\pm 6.34\%$) in Caucasians. Participants were asked to continue with normal daily activities and record any abnormalities such as visual disturbances, headache, nausea, fainting, palpitations, physical activity and emotional stress on their ambulatory diary cards. The data were analysed using the CardioVisions 1.15.2 Personal Edition software (Meditech[®]). Hypertension status was defined according to the European Hypertension Society guidelines for ambulatory BP: SBP \geq 130 and / or DBP \geq 80 [16].

Anthropometric measurements

Participants' waist circumferences were measured to the nearest 0.1 cm using the standardized methods of the International Society for Advancement of Kinanthropometry (ISAK) [17].

Cognitive distress

A cognitive perception of own well-being (cognitive distress) was derived from the 28-item General Health Questionnaire (GHQ), that was developed as a measure of common mental health problems of depression, anxiety, somatic symptoms and social withdrawal [18]. Any scoring exceeding the threshold value of 4 is classified as "psychiatric caseness", meaning that these individuals qualify for further clinical attention [19].

Biochemical measurements

A sterile winged infusion set was used to obtain blood samples from the antebraial vein branches by a registered nurse and handled according to standardized procedures and stored

at -80°C until analysis. Fasting samples for gamma glutamyl tranferase (γ -GT) were analysed using the sequential multiple analyser computer (Konelab 20i; Thermo Scientific, Vantaa, Finland). Serum cotinine levels were determined with a homogeneous immunoassay (Automated Modular, Roche, Basel, Switzerland). HIV-status was measured using the First Response kit (Premier Medical Corporation, India) as well as the confirmatory Pareekshak test (Bhat Biotech, India).

Serum samples were analysed for cortisol using an electro chemiluminescence immunoassay with the Elecsys 2010 apparatus (Roche, Basel Switzerland). Telomere samples were obtained from peripheral blood mononuclear cells (PBMC) that were isolated by density gradient centrifugation from each blood sample. DNA was extracted from the PBMC using the PureGene DNA isolation system. The exact protocol for measuring telomere lengths is described elsewhere [20]. Measurement of relative telomere lengths (Telomere PCR to single-copy gene PCR or T/S ratio) was determined by quantitative real-time polymerase chain reaction (RT-PCR) as described by Cawthon [21].

PA measurement

The weekly habitual PA of participants was measured over a period of seven consecutive days with an Actiheart (GB0/67703[®], CamNtech Ltd., Cambridgeshire, UK). All the raw 24-hour recordings (seven-days) of each participant were visually inspected to distinguish between time awake (including sedentary hours), and time asleep. To differentiate sleeping time from sedentary time, heart rate (HR) was considered along with the Metabolic Equivalent of Task (MET, 1 MET regarded as being asleep) and activity level. Where the HR in the evenings gradually dropped (over a period of 15 or more epochs) to less than the average HR in a selected sedentary sample period and activity level was equal to zero, the participant was considered to be sleeping. The end of sleeping could clearly be seen by an immediate increase in the HR of more than 10 to 20 beats per minute relative to preceding sleeping HR, as well as a corresponding increased MET- and activity-level. Habitual PA during the daily awake minutes was categorised according to daily awake sedentary time (≤ 1.5 METs), daily awake light activity time (> 1.5 & < 3 METs), daily awake moderate activity time (≥ 3 & < 6 METs) and daily awake vigorous activity time (≥ 6 METs) [22].

4.2.3 Data-collection procedure

Clinical assessments were performed over a 2-day period per person and the participants stayed overnight in a well-controlled environment at the Metabolic Unit Research Facility of the North-West University (NWU). On day 1 at 07h00, the Cardiotens apparatus (24-h ambulatory BP) was fitted to four participants at their selected schools. Participants then resumed their normal daily activities and were transported to the university at approximately 15h00 for further clinical assessments. They were introduced to the experimental set-up to lessen anticipation stress [23]. The participants enjoyed a standardized dinner at around 18h00, completed psychological questionnaires under supervision of a clinical psychologist and were asked to refrain from taking any beverages after 22h00.

Participants were woken at 07h00 on day 2, the Cardiotens apparatus was disconnected and their anthropometric measurements taken. A resting 12-lead ECG was performed after each participant had rested in the semi-recumbent position for half an hour and blood sampling commenced one hour later to avoid the cortisol awakening response [24]. A 65 ml blood sample was obtained in standard 10 ml EDTA-treated vacutainer tubes by a registered nurse from the brachial vein branches of the dominant arm using a winged infusion set and was immediately sent to the laboratory for storage. The participants then showered and the Actiheart device for the seven-day PA measurement was fitted. Each participant was given four extra electrodes, as well as plaster to immediately secure the Actiheart back onto the chest if it became disconnected during the course of the seven days. Participants were instructed to carry on with their habitual daily activities wearing the monitor at all times whilst awake and asleep. The Actiheart was collected from each participant at the various schools on the eighth day and downloaded onto a computer for storage, viewing and analysis.

4.2.4 Statistical analyses

Statistical analyses were performed with the Statistica 12 (StatSoft Inc., 2014) programme. Data normality was evaluated using both the Shapiro-Wilk test and Quantile-Quantile plots. Gamma glutamyl transferase (γ -GT) was normalized by log transformation and serum cotinine was categorized. Moderate and vigorous activity time was not log-transformed as all residual plots of the multivariate regression analyses that included these two measures indicated normal distribution. One-way analyses of covariance (ANCOVA) were used to determine significant ethnic differences in physiological, anthropometric and physical

activity measures adjusting for covariates age and log γ -GT. Multivariate regression analyses were computed. Firstly, a forward stepwise regression analysis evaluated the associations with serum cortisol (dependent marker), adjusting for race, sex, age, cardiovascular- and/or kidney disease, hypertension- and/or diabetes drug use, log γ -GT, smoking, waist circumference, ROS, MAP, estradiol, GHQ total score and time spent in different MET-categories (each entered separately into the model). Partial correlations, adjusted for age and log γ -GT were used to assess if any relationship between time spent in the different MET-categories and cognitive stress (GHQ total score) exist. A second forward stepwise regression analysis determined associations with telomere length (dependent marker), adjusting for race, sex, age, cardiovascular and/or kidney disease, hypertension and/or diabetes drug use, γ -GT, smoking, waist circumference, cortisol, GHQ total score, ROS, mean arterial pressure (MAP) and time spent in different MET-categories (each entered separately into the model). Despite the race interaction observed with telomere length, the separate groups did not comply with sample size requirements as calculated by the formula of Tabachnick and Fidell as quoted by Pallant [25]: $N > 50 + 8m$ (where m = the number of independent variables). The regressions were therefore performed for the group as a whole (Africans and Caucasians combined), entering race as an independent variable. Lastly, a sensitivity analysis (partial correlations adjusted for age, log γ -GT and cortisol) assessed whether any of the different MET-categories were associated with waist circumference (a variable associated with both cortisol and telomere length) in this study population. Data were considered statistically significant for all the analyses at $p \leq 0.05$.

4.3 RESULTS

The study population consisted of African men ($n=45$), African women ($n=51$), Caucasian men ($n=52$) and Caucasian women ($n=55$). The average GHQ total score for this study population was above the clinical threshold of 4 [19], indicating high levels of cognitive stress – less than half of the participants scoring below 4 ($n=99$, 49%) (Table 4.1). More than half of the participants could be classified as hypertensive according to the European guidelines for ambulatory blood pressure [16], however, not all hypertensive participants used anti-hypertensive drugs. The average daily awake time of the group was slightly over 17 hours per 24-hour cycle. Although the habitual PA time spent in light and moderate activity may seem high, it accumulated during an average uninterrupted wearing period of

17.07 awake hours in which activity was recorded every minute (one-minute epoch intervals). Almost half of this awake time (45.66%) was spent sedentarily.

Table 4.1: Descriptive statistics of the study population

| | Total population (N=203) |
|--|------------------------------------|
| Characteristics (<i>Unadjusted Analysis</i>) | Mean ± SD |
| African participants, n (%) | 96 (47.29) |
| Caucasian participants, n (%) | 107 (52.71) |
| Age (years) | 49.77±8.57 |
| Telomere length (ng/μl) | 0.96±0.27 |
| Cortisol (nmol/l) | 235.14±94.74 |
| GHQ total score | 6.09±6.36 |
| Waist circumference (cm) | 96.38±15.77 |
| γ-GT (U/l) | 42.28±57.68 |
| Smoking, n (%) | 24 (11.82) |
| ROS (1 Unit=10 mg/l H ₂ O ₂) | 79.88±22.82 |
| 24-h SBP (mmHg) | 128.89±17.01 |
| 24-h DBP (mmHg) | 79.42±10.49 |
| Mean arterial pressure | 95.92±12.24 |
| Hypertensive (SBP≥130 and / or DBP≥80), n (%) | 105 (51.72) |
| Anti-hypertensive and / or anti-diabetic drugs, n (%) | 69 (33.99) |
| Kidney disease history, n (%) | 9 (4.43) |
| CVD history, n (%) | 29 (14.29) |
| Physical activity measurements (<i>Unadjusted Analysis</i>) | Mean ± SD |
| Average Actiheart wear time (days) | 6.84±0.32 |
| Daily awake time (average minutes per 24-hour cycle) | 1024.23±64.90 |
| Sedentary time, minutes (% of awake time) | 467.66 (45.66) |
| Light activity time, minutes (% of awake time) | 375.75 (36.69) |
| Moderate activity time, minutes (% of awake time) | 175.39 (17.12) |
| Vigorous activity time, minutes (% of awake time) | 5.43 (0.53) |

GHQ, General Health Questionnaire ; γ-GT, Gamma Glutamyl Transferase; ROS, Reactive Oxygen Species; SBP, Systolic blood pressure ;

DBP, Diastolic blood pressure; CVD, Cardiovascular disease.

Significant race interactions were observed with telomere length ($F(1, 176); 25.31, p \leq 0.000$). Independent T-tests revealed significant ethnic differences in mean age ($p=0.024$) and serum γ -GT ($p \leq 0.000$) – with the Africans being slightly younger (Africans = 48.33 years; Caucasians = 51.06 years) but with a much higher alcohol consumption (Africans = 59.84 U/L; Caucasians = 27.02 U/L). When adjusting for age and log γ -GT, the Africans had significantly shorter telomeres, as well as significantly higher cognitive distress (GHQ total scores) and ambulatory blood pressure (24-h SBP, DBP and MAP) than the Caucasians (Table 4.2). Both groups presented with a GHQ score above 4, however, only the African population presented with elevated 24-h SBD and DBP levels.

Table 4.2: ANCOVAS indicating ethnic differences in participant characteristics

| | Africans (n=96) | Caucasians (n=107) | P-value |
|--|-------------------------|-------------------------|----------------|
| Variables, Mean ($\pm 95\%$ CI) | | | |
| Telomere length (ng/ μ l) | 0.84 (0.79, 0.89) | 1.06 (1.01, 1.10) | $\leq 0.000^*$ |
| Serum cortisol (nmol/l) | 219.83 (199.94, 239.73) | 248.02 (229.50, 266.54) | 0.053 |
| GHQ total score | 7.80 (6.48, 9.12) | 4.62 (3.39, 5.85) | 0.001* |
| Waist circumference (cm) | 97.47 (94.32, 100.61) | 95.09 (92.16, 98.01) | 0.300 |
| 24-h SBP (mmHg) | 135.06 (131.91, 138.20) | 123.21 (120.29, 126.14) | $\leq 0.000^*$ |
| 24-h DBP (mmHg) | 82.66 (80.69, 84.59) | 76.49 (74.67, 78.30) | $\leq 0.000^*$ |
| MAP (mmHg) | 100.12 (97.88, 102.37) | 92.06 (89.97, 94.15) | $\leq 0.000^*$ |
| ROS (1 Unit = 1.0 mg/l H ₂ O ₂) | 80.14 (75.19, 85.09) | 79.91 (75.27, 84.54) | 0.948 |

Adjusted for covariates age and log γ -GT. * = Statistical significance is considered when $p \leq 0.05$. GHQ, General Health Questionnaire; SBP, Systolic blood pressure, DBP, Diastolic blood pressure; MAP, Mean arterial pressure; ROS, Reactive Oxygen Species.

Although no significant ethnic differences were detected for the awake time spent in different MET-categories, the Africans spent nearly an hour more of the average daily awake time sedentary (54.77 minutes) than the Caucasians (Figure 4.1). Light activity time was more or less the same for the two groups, while the average daily awake moderate activity time was higher in the Caucasians. Both groups recorded less than 10 minutes of daily awake vigorous activity time.

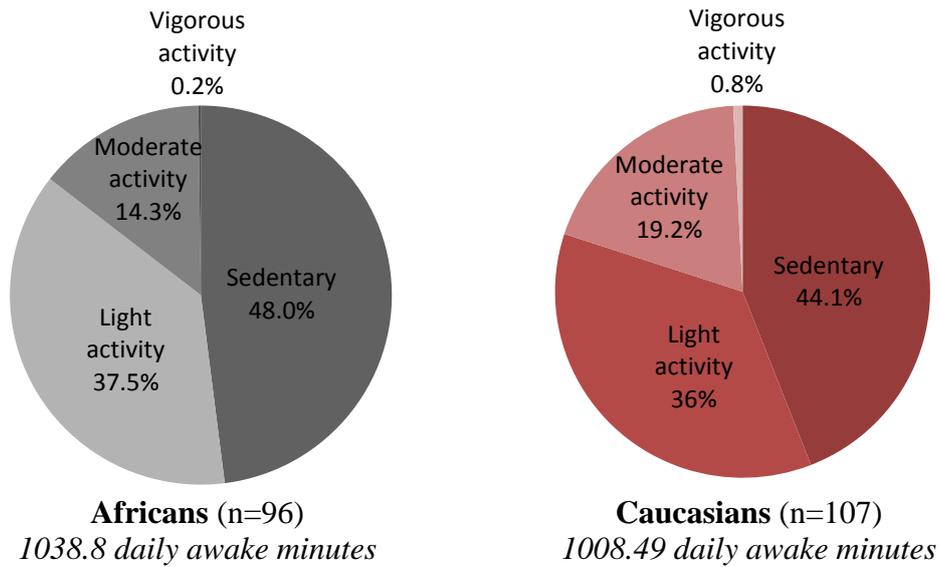


Figure 4.1: Average percentage of daily awake time spent in different MET-categories for the African and Caucasian populations

Including race and sex in the models, forward stepwise regressions evaluated the associations between various physiological, biochemical and lifestyle characteristics (including habitual PA) with serum cortisol (Table 4.3, Adjuster $R^2=0.23$). All the models (MET-categories were each entered separately into the model) had the same outcome – indicating significant positive associations with log γ -GT and ROS and also a significant negative association with waist circumference. No associations were observed with ethnicity and sex. None of the PA MET-categories entered the cortisol models and partial correlations (adjusted for age and log γ -GT) also did not show any PA associations with the GHQ scores. Cognitive distress (GHQ total scores) entered the models, but was not associated with the serum cortisol levels.

Table 4.3: Forward stepwise regression analyses results examining associations between cortisol and selected physiological, biochemical and lifestyle biomarkers

| | Total group (N=167) | |
|--|--------------------------|----------------|
| | β ($\pm 95\%$ CI) | P-value |
| Models statistics $F(13, 153)=4.60, p<0.000, Adjusted R^2 = 0.23$ | | |
| Log γ -GT | 0.23 (0.07, 0.40) | 0.007* |
| ROS (1 Unit = 1.0 mg/1 H ₂ O ₂) | 0.31 (0.18, 0.46) | $\leq 0.000^*$ |
| Waist circumference (cm) | -0.24 (-0.41, -0.09) | 0.005* |
| MAP (mmHg) | -0.16 (-0.31, 0.02) | 0.059 |
| CVD and/or kidney disease | -0.10 (-0.24, 0.04) | 0.183 |
| Age (years) | 0.10 (-0.04, 0.03) | 0.183 |
| GHQ total score | 0.08 (-0.07, 0.24) | 0.286 |

*=Statistical significance is considered when $p \leq 0.05$. γ -GT, Gamma Glutamyl Transferase; ROS, Reactive Oxygen Species; MAP, Mean arterial pressure; CVD, cardiovascular disease; GHQ, general health questionnaire. Additional covariates considered for models: race, sex, age, hypertension- and/or diabetes drug use, smoking, Estradiol, Time spent in different MET-categories (each entered separately into the model).

Unadjusted analyses (Pearson's correlation matrices) with the main dependent in the total group revealed shorter telomeres were significantly associated with an older age ($r=-0.25, p=0.001$), greater waist circumference ($r=-0.27, p=0.004$), greater log γ -GT ($r=-0.35, p \leq 0.000$) as well as higher 24-h SBP ($r=-0.22, p=0.007$), 24-h DBP ($r=-0.18, p=0.028$) and MAP ($r=-0.20, p=0.012$). No significant relations were observed with the time spent in the different MET-categories and telomere lengths.

Race and sex, as well as disease and medication use, were included as covariates in forward stepwise regression models to assess associations with telomere length (Table 4.4). Significant negative associations were indicated with age, log γ -GT and waist circumference that is in accordance with the above mentioned correlations. In contrast with the Pearson correlations, the MAP now indicated a positive association, along with ROS. The four models used (entering sedentary time, light activity-, moderate activity- and vigorous activity time separately) explained between 34% and 35% of the variance in telomere length and all four models indicated similar significant covariates. Table 4.4 also shows that ethnicity is associated with telomere length.

Table 4.4: Forward stepwise regression analyses results examining associations between telomere length and selected physiological, biochemical and lifestyle biomarkers

| | Total group | |
|---|----------------------|----------------|
| | (N=190) | |
| | β (±95% CI) | P-value |
| Models statistics $F(9, 180)=12.30, p<0.000, Adjusted R^2 = 0.34-0.35$ | | |
| Race | 0.47 (0.34, 0.60) | ≤0.000* |
| Age (years) | -0.28 (-0.40, -0.16) | ≤0.000* |
| Log γ-GT | -0.21 (-0.36, -0.08) | 0.003* |
| ROS (1 Unit = 1.0 mg/l H ₂ O ₂) | 0.14 (0.02, 0.26) | 0.022* |
| MAP (mmHg) | 0.17 (0.01, 0.32) | 0.032* |
| Waist circumference (cm) | -0.17 (-0.30, -0.03) | 0.017* |
| Cortisol (nmol/l) | -0.12 (-0.24, 0.00) | 0.068 |
| Sedentary time (minutes) | 0.12 (-0.06, 0.24) | 0.061 |
| Light activity time (minutes) | -0.09 (-0.21, 0.03) | 0.140 |
| Moderate activity time (minutes) | -0.08 (-0.20, 0.04) | 0.183 |
| Smoking | -0.07 (-0.20, 0.04) | 0.151 |

*=Statistical significance is considered when $p \leq 0.05$. γ-GT, Gamma Glutamyl Transferase; ROS, Reactive Oxygen Species; MAP, Mean arterial pressure. Additional covariates considered in the four models: sex, cardiovascular- and/or kidney disease, hypertension- and/or diabetes drug use, smoking, GHQ total score, Time spent in different MET-categories (each entered separately into the model).

None of the MET-categories indicated any significant associations with either cortisol or telomere length (Tables 4.3 and 4.4). However, partial correlations (adjusting for age, log γ-GT and cortisol) revealed a significant negative relationship between waist circumference and daily awake time spent in light activity ($r=-0.21, p=0.004$) – in other words, more light activity during the day results in a lower central obesity. Although not the main aim of this study, this relationship was assessed as waist circumference showed significance in all regression models and a greater waist circumference was also shown to be associated with higher 24-h MAP for the group in total, as well as in both ethnic groups (Total group, $r=0.40, p=0.000$; Africans, $r=0.28, p=0.008$; Caucasians, $r=0.54, p \leq 0.000$).

4.4 DISCUSSION

The present study aimed to investigate the associations between habitual PA, cognitive distress and telomere shortening in African and Caucasian teachers. There were no differences in PA measures between Africans and Caucasians, but Africans presented with significantly higher 24-h ambulatory blood pressure (SBP, DBP and MAP). This more vulnerable African group had significantly shorter telomere lengths than the Caucasians (even after adjusted for age and log γ -GT). They also showed higher cognitive distress levels with attenuated or possible down-regulated cortisol levels. A study investigating telomere length in healthy Caucasian and African-American adolescents indicated that the African-American adolescents had longer telomeres than their Caucasian peers [26]. Exploring racial effects on telomere length, Hunt and colleagues found that African-Americans had longer leukocyte telomeres than Caucasians at nearly all ages. Telomere shortening (adjusted for sex and BMI) was, however, at a steeper slope in the African-Americans [27].

Time spent in the four PA MET-categories did not indicate any associations with cortisol or telomere length in the current study population. This is contradictory to some studies indicating participation in regular moderate or vigorous levels of PA to be associated with attenuation in telomere erosion or to buffer the detrimental effects of chronic stress on cellular longevity [11, 13, 28, 29, 30, 31]. Cherkas and colleagues reported that the telomere lengths of individuals participating in leisure time PA for 199 minutes and more per week were found to be the same as sedentary individuals ten years younger [11]. These findings were strengthened by research on sets of twins showing that the leukocyte telomere length of the more active twin was on average longer than the less active twin [11]. A major limitation of many of these studies is the use of self-reported PA that is likely to introduce measurement error and cannot account for 24-h time use, thus negating the influence of sedentary time and light intensity activity.

The evidence regarding PA and cortisol remains controversial. Although there was no significant difference in time spent in different MET-categories between the two ethnic groups, the Africans on average recorded 54.77 more daily awake sedentary minutes and 45.08 minutes less moderate intensity activity time than the Caucasians. Indeed, the accumulation of time spent in different MET-categories was high in both groups due to recording during the average 17-h awake time. Although none of the PA MET-categories

was associated with cognitive distress, the scores of the Africans were significantly higher than those of the Caucasians. Rimmele *et al.* demonstrated reduced physiological (salivary cortisol levels and heart rate) and psychological (calmer mood prior to stressor and less anxiety throughout stressor) stress responsiveness in trained men compared to untrained men [32]. This is, however, contradictory to a more recent study where no associations were indicated between stress responses (during the stress task and recovery) and both self-report and objective measures of physical activity [33].

Shorter telomeres were associated with an older age, alcohol abuse and increased central obesity in the current study. Despite the elevated cognitive distress levels observed in both ethnic groups (especially the Africans), attenuated cortisol levels were observed. Cognitive distress did not indicate associations with telomere shortening, however, the attenuated cortisol levels showed a tendency towards associations with longer telomere length. Similar findings were indicated by research of Epel and colleagues, where telomere shortening was related to stress arousal (increased cortisol, epinephrine and norepinephrine), but not with negative mood [7]. It was previously indicated that urbanized living is not only associated with decreases in PA, but is accompanied by insecurities and disruption that contribute to additional psychological stress [34]. Chronic psychosocial stress has the potential to contribute to an increased oxidative stress burden by chronic activation of the autonomic and neuroendocrine stress response systems [6]. One could therefore argue that cortisol levels might be down-regulated in the current study population as a protective mechanism of the human body against chronically high autonomic stress responses. A number of studies previously suggested that the adrenal gland becomes hypoactive in chronic stress-related states and due to the down-regulation of the cortisol receptors, hypocortisolism in chronic stress may occur [35, 36]. Hellhammer *et al.* found that although hypocortisolemic subjects scored high on measures of depression, perceived stress and physical complaints, they did not show allostatic load [37]. This indicates that a hypocortisolemic stress response may have a protective role on cardiovascular and metabolic disorders [37]. Our data support this mechanism as attenuated cortisol levels were associated with significantly decreased ROS and showed a tendency to be associated with longer telomeres.

Both the African and Caucasian participants in the current study spent more than 35% of their awake time doing activities of light intensity. This was also the only MET-category associated with smaller waist circumferences when observing the group in total and lower

central obesity was associated with longer telomeres. It is therefore possible that increased daily light activity time could be beneficial by lowering central obesity – thus having an indirect protective effect on telomere shortening. A review of physical activity and telomere biology indicated that exercise slows or prevents the symptoms of age-related diseases and is therefore able to indirectly alter telomere biology and reduce disease risk [9]. Long-term exercise (moderate intensity treadmill walking for 45 minutes, three times per week for six months) down-regulated oxidative stress in obese women and although not significant, the rate of telomere shortening was slower in the exercise group than in their controls. This research also stated that exercise-induced variations in antioxidant enzymes may be relevant in maintaining telomere lengths [38].

4.5 STUDY STRONG POINTS AND LIMITATIONS

The average Actiheart wear time of the current study population was 6.84 days and awake and sleep time carefully separated. Using time spent in the different PA MET-categories captured during true awake time (17 hours per 24-h cycle) for associations with physiological and biochemical markers for disease in two different ethnic groups from homogeneous economic status (all South African teachers), contributes to the uniqueness of this study. The cross-sectional design, however, prevents us from inferring causal links from the data. Individual calibrations prior to fitting the Actiheart devices were not performed due to the high clinical cardiovascular disease risk of many participants [39] - thus self-reported PA was used instead to choose a physical activity level on the Actiheart programme.

4.6 CONCLUSION

There was no association between habitual PA (expressed as time spent in different MET-categories) with either cortisol or telomere length in the current study. Shorter telomeres were associated with older age, increased alcohol consumption and higher central obesity. A tendency towards shorter telomeres with increased cortisol was also observed. Doing more daily activities of light intensity was, however, associated with a lower central obesity. This suggests that habitual physical activities of light intensity could indirectly contribute to lessen DNA damage as waist circumference showed a significant direct negative association with telomere length. Waist circumference also indicated strong positive correlations with the 24-

h MAP in both ethnic groups. Therefore, increasing daily awake light activity should be incorporated into lifestyle modification programmes for health promotion. Limiting alcohol use is strongly recommended, as log γ -GT was associated with both the cortisol and telomere length in this population. Further research is required to investigate adrenal gland and sympathetic activity responses to chronic stress and the long-term effect on health. Also, intervention studies, incorporating lifestyle changes such as long-term PA of light intensity, should be conducted to explore the effect of such lifestyle changes on chronic stress responses and age-related disease in different ethnic groups.

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CHAPTER 5

Two days of Actiheart wear time sufficient to predict weekly energy expenditure and habitual physical activity

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ABSTRACT

Background: The participant burden of physical activity measuring devices, such as the Actiheart, is high, with limited research regarding minimum wear time in diverse ethnic groups. **Methods:** This study aimed at determining the minimum Actiheart wear time to accurately estimate energy expenditure and habitual physical activity in urban African and Caucasian school teachers (n=216) of the SABPA prospective cohort study. Intraclass correlation coefficients (ICC) indicated the level of agreement between the 24-h total energy expenditure (TEE) across the seven different weekdays and within all 35 combinations of consecutive weekdays. Deviations from the weekly average TEE and awake time spent in different metabolic equivalent of task (MET) categories were also determined. **Results:** High agreement (ICC) was obtained between the average 24-h TEE of different weekdays and within all the 2, 3, 4, 5 and 6 consecutive day combinations ($\rho\text{-square} \geq 0.9$). However, only the Wednesday-to-Thursday combination did not significantly differ from the weekly average for awake time spent in all the different MET-categories. **Conclusion:** The two-day combination of Wednesday-to-Thursday deviated least from the weekly average TEE, as well as awake time spent in different MET-categories in all ethnic and sex groups. Using this combination may help reduce the participant burden of the Actiheart device.

Key words: *physical activity measures, human energy expenditure, accelerometry in adults, Actiheart*

5.1 INTRODUCTION

Although self-report measures of physical activity (PA), such as the International Physical Activity Questionnaire (IPAQ) and Global Physical Activity Questionnaire (GPAQ), are standardized and validated,^{3,10} these instruments are inherently limited by various biases. The contributors to measurement errors include individual recall bias, daily and seasonal variability in PA patterns and different interpretations of intensity of activity due to differences in human perception and lack of education.^{7,21} Objective measures such as pedometers, accelerometers, heart rate monitors or combined accelerometer and heart rate monitors have been widely used in an attempt to eliminate the self-report method bias.^{12,20,29} However, it was previously indicated that the participant burden of a heart rate monitor heightened after a wear period of four days due to skin irritation.²⁸ Participant compliance with wearing objective devices is extremely important to ensure credible PA data.⁹ Research regarding the minimum wear time required to limit participant burden while still ensuring reliable PA data obtained from some of these objective instruments is lacking.⁵

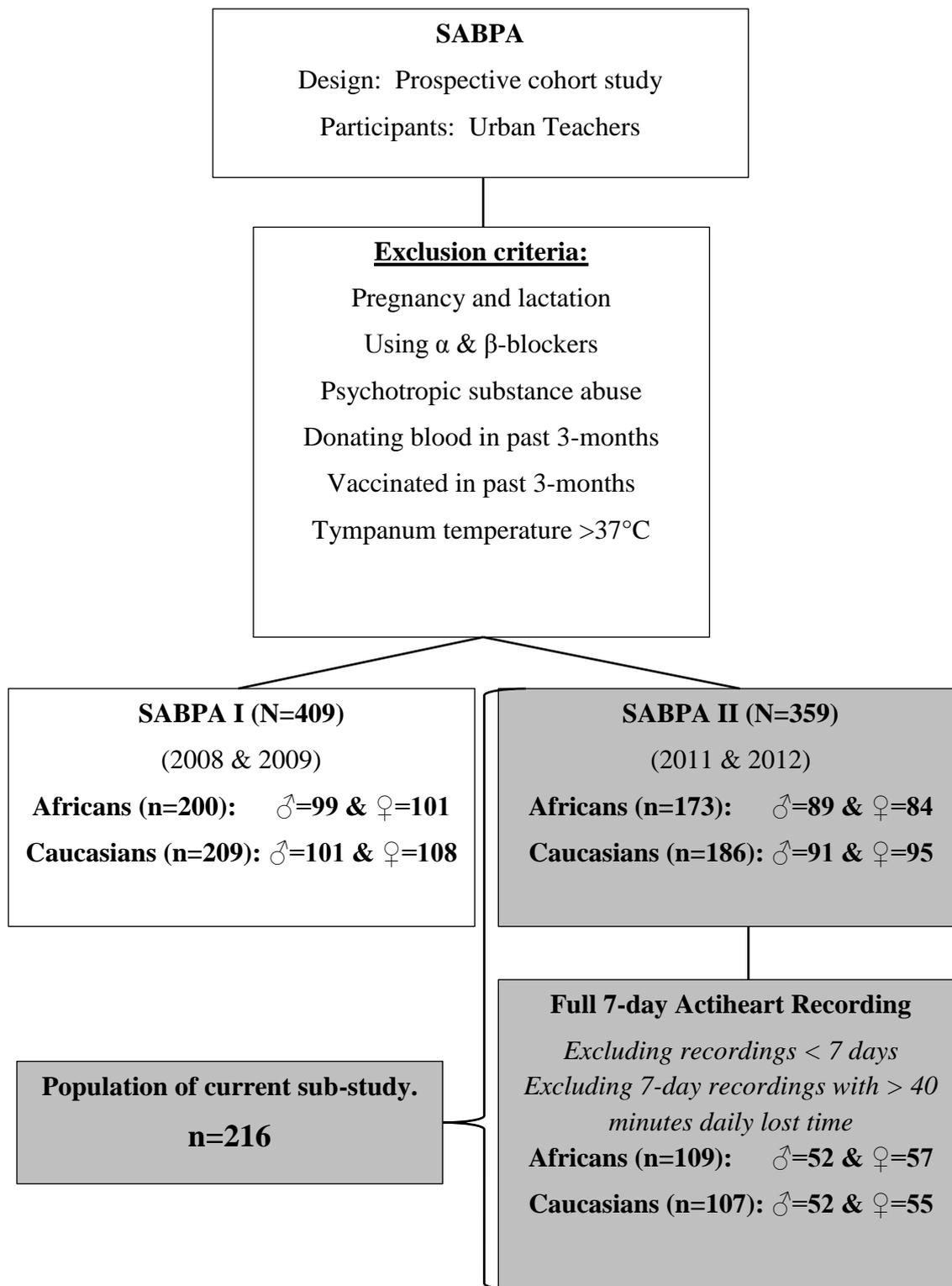
The Actiheart (a combined accelerometer and heart rate sensor) has been validated against indirect calorimetry^{6,8,19,23} and established as a valid tool to estimate daily free-living (habitual) physical activity energy expenditure in sub-Saharan Africans.⁴ This device is also waterproof and does not need to be removed, except when replacing the electrodes – therefore total energy expenditure (TEE) can be measured in free-living conditions, rather than only the daily physical activity energy expenditure (PAEE).^{20,29} This device is therefore ideal to use in the diverse South African setting. The authors of the current study are unaware of any attempt to establish the minimum wear time of the Actiheart device in an adult population. This study therefore aimed to ascertain the minimum number of consecutive days the Actiheart should be worn to reliably estimate energy expenditure and habitual physical activity in a cohort of African and Caucasian teachers.

5.2 METHODS

5.2.1 Study design and participants

This sub-study formed part of the Sympathetic activity and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study with a target population of urban African and Caucasian school teachers from the Dr Kenneth Kaunda Education District in the North West Province of South Africa. Permission for the study was obtained from the North West Department of Education, as well as the South African Democratic Teachers' Union and all participants signed informed consent prior to the start of data collection. The SABPA study conforms to the principles outlined in the Declaration of Helsinki (revised 2004) and was approved by the Ethics Committee of the North-West University, South Africa (0003607A6). The cohort profile of the SABPA study is well explained in a publication of Malan and colleagues.¹⁷

The follow-up data of the SABPA study (N=359) were used for the purpose of this sub-study. Data collection commenced during February to May in 2011 (African teachers, n=173) and again in 2012 (Caucasian teachers, n=186), avoiding seasonal influences. Only 60% (n=216) of these participants complied with wearing the Actiheart for a full seven days and with less than 40 minutes improper Actiheart contact time. Colley *et al.* stated that findings of allowable interruption periods (lost and non-wear time) when using accelerometry are inconsistent in literature.⁹ Using an interruption period of less than 40 minutes per day as part of the exclusion criteria would have negatively affected the sample size of the current study. Prior to calculating the actual Actiheart wear time of each participant, the non-contact minutes were deducted from the total time recorded. The participants, as well as inclusion and exclusion criteria are explained in Figure 5.1.



α, Alpha; β, Beta; ♂, men; ♀, women

Figure 5.1: Description of the study population and exclusion criteria

5.2.2 Measurements and equipment

Anthropometric measurements

The participants wore minimal clothing for the anthropometric measurements.²⁵ Their body mass index (BMI) ($\text{kg}\cdot\text{m}^{-2}$) was calculated by dividing body weight in kilograms by height in metres squared.^{2,25} Intra- and inter-observer variability was less than 10%.

Biochemical measurements

A sterile winged infusion set was used to obtain blood samples from the antebachial vein branches by a registered nurse and handled according to standardized procedures and stored at -80°C until analysis. Fasting samples for gamma glutamyl transferase (γ -GT) were analysed using the sequential multiple analyser computer (Konelab 20i; Thermo Scientific, Vantaa, Finland). HIV status was measured using the First Response kit (Premier Medical Corporation, India) as well as the Pareekshak test (Bhat Biotech, India).

Habitual energy expenditure and physical activity measurement

The weekly habitual energy expenditure (EE) and PA of participants were measured over a period of seven consecutive days with an Actiheart[®] (GB0/67703, CamNtech Ltd., Cambridgeshire, UK). The resting heart rate, obtained from the resting 12-lead electrocardiogram (NORAV Medical Ltd PC 1200, software version 5.030, Kiryat Bialik, Israel) performed under supervision of a registered nurse, was used to calculate the sleep heart rate required by the Actiheart programme when the device was fitted to each participant. Although individual calibration by means of a step test was not performed due to the high cardiovascular risk profile of various participants, as well as the time restriction in terms of data collection, a Biokineticist (Clinical Exercise Physiologist) thoroughly questioned participants regarding their current daily and weekly PA behaviour before an activity level option was chosen on the Actiheart programme.

Heart rate (HR) was considered along with the metabolic equivalent of task (MET, 1 MET regarded as being asleep) and activity level, to differentiate sleeping time from being awake. Where the HR in the evenings gradually dropped (over a period of 15 or more epochs) to less than the average HR in a selected awake time sedentary sample period, and the activity level was equal to zero, the participant was considered to be sleeping. The end of sleeping could

clearly be seen by an immediate increase in the HR of more than 10 to 20 beats per minute (bpm) relative to preceding sleeping HR, as well as an increased MET- and activity-level.

The total energy expenditure (TEE) of an individual, expressed in kilocalories (kcal), is composed of the resting energy expenditure (REE), dietary-induced energy expenditure (DEE) and the activity-induced energy expenditure (AEE).²⁷ Therefore, for the purposes of the present analysis, the average 24-h TEE of each day of the week, as well as different combinations of consecutive weekdays, was compared to the weekly average TEE, as daily variations in dietary intake, as well as activities would influence the TEE per 24-h cycle. PA during awake hours is expressed in daily time spent in different intensities of activity. The following MET-categories were derived: awake sedentary time (≤ 1.5 METs), awake time spent in light activity (> 1.5 & < 3 METs), awake time spent in moderate activity (≥ 3 & < 6 METs) and awake time spent in vigorous activity (≥ 6 METs).¹

5.2.3 Data-collection procedure

Data were collected in four participants per weekday from February to May. Clinical assessments in a fasting state were performed over a 2-day period, with participants staying overnight in a controlled environment at the Metabolic Unit Research Facility of the North-West University (NWU). At approximately 10h00 on the morning of the second day, after completing anthropometric measurements, ECG-recordings and blood sampling, an Actiheart device was fitted to each participant. Participants were instructed to carry on with their habitual daily activities wearing the monitor at all times whilst awake and asleep. Each participant was provided with 4 extra electrodes, as well as plaster to ensure that the Actiheart was immediately refitted if electrodes became disconnected during the course of the seven-day recording.

5.2.4 Data analyses

Statistical analyses were performed with the Statistica 12 (StatSoft Inc., 2014) and the SPSS Statistics 22.0 programmes (IBM[®], 2013). Independent t-tests, chi-square analyses and ANCOVAS (adjusted for age and log γ -GT in men and BMI and log γ -GT in women) were used to describe differences and proportions in the basic characteristics, as well as in the various Actiheart measurements between African and Caucasian participants. The number of days needed to achieve a targeted reliability, i.e. 0.8, was determined directly by computing

Intra-Class Correlations (ICC), a special case of the one-facet generalizability study.²⁴ We conducted ICC analyses for the average 24-h TEE of all seven weekdays, as well as for all 35 consecutive day combinations (2-day, 3-day, 4-day, 5-day and 6-day combinations) to determine the number of days of monitoring to achieve an ICC value of 0.8 (strong level of agreement).^{4,24} The ICC analyses involved a mixed-model framework where random effects were assumed for the subjects and fixed effects for the days. Thereafter, dependent t-tests were performed separately for all sex and ethnic groups to determine whether the average TEE over a 24-h cycle of the different individual weekdays (Monday to Sunday), as well as the average TEE of all 35 consecutive day combinations, significantly deviated ($p \leq 0.05$) from the weekly average TEE. Lastly, dependent t-tests were used to determine whether the average daily time spent in different MET-categories when awake in the chosen sample of minimum wear time, significantly differed ($p \leq 0.05$) from the daily average awake time spent in the MET-categories of the 7-day recording.

5.3 RESULTS

Table 5.1 indicates the differences in age and lifestyle behaviours between African and Caucasian teachers. The African men were significantly younger than the Caucasian men, whilst the African women had significantly higher BMI-values than the Caucasian women. Both the African men and women respectively consumed significantly more alcohol (serum γ -GT) than the Caucasian men and women. Thirteen of the African participants included in this sub-study were HIV⁺.

Table 5.1: Basic characteristics of the African and Caucasian teachers

| | African men (n=52) | Caucasian men (n=52) | p-value (p≤0.05) |
|-------------------------------------|--------------------------------|----------------------------------|----------------------------|
| Lifestyle factors, Mean ± SD | | | |
| Age (years) | 48.00 ± 7.71 | 51.58 ± 8.91 | 0.031* |
| BMI (kg/m ²) | 28.83 ± 5.55 | 29.29 ± 3.89 | 0.626 |
| γ-GT (U/L) | 87.28 ± 91.47 | 36.15 ± 33.34 | ≤0.000* |
| Smoking , N (%) | 13 (25) | 8 (15.38) | 0.222 |
| HIV+ (N, %) | 7 (13.46) | 0 (0.00) | 0.006* |
| | African women (n=57) | Caucasian women (n=55) | p-value (p≤0.05) |
| Lifestyle factors, Mean ±SD | | | |
| Age (years) | 48.57± 8.43 | 50.56 ± 8.39 | 0.214 |
| BMI (kg/m ²) | 33.13 ± 7.48 | 26.02 ± 6.29 | ≤0.000* |
| γ-GT (U/L) | 35.99 ± 34.02 | 18.38 ± 22.81 | 0.002* |
| Smoking , N (%) | 4 (7.02) | 5 (9.09) | 0.687 |
| HIV+ (N, %) | 6 (10.53) | 0 (0.00) | 0.013* |

* = Statistical significant ethnic differences (p≤0.05). Where BMI is Body Mass Index and γ-GT (U/L), Gamma Glutamyl Transferase.

Table 5.2 describes the average Actiheart wear time for each ethnic and sex group. There were no significant differences in Actiheart measures between the two male ethnic groups, with both groups showing an average recording time of 6.9 days. The average number of recorded days in African women was closer to a full seven days than in the Caucasian women (6.9 and 6.7 days respectively), with all recordings showing significant differences between these two ethnic groups. According to the average MET-levels, daily awake time was mostly spent sedentary in African men (53.24%), Caucasian men (50.88%) and African women (47.65%). Caucasian women (35.93%) indicated the least sedentary time during awake hours.

Table 5.2: Basic adjusted measures of the seven-day Actiheart recording in an African and Caucasian cohort

| | African men (n=52) | Caucasian men (n=52) | P-value |
|---|--------------------------------|----------------------------------|----------------|
| Variables, Mean (\pm95% CI) | | | |
| Recorded days (Lost time excluded) | 6.99 (6.88-6.96) | 6.89 (6.85-6.93) | 0.343 |
| Average awake hours (24-hour cycle) | 17.12 (16.79-17.46) | 16.79 (16.46-17.12) | 0.194 |
| Average sleep hours (24-hour cycle) | 6.88 (6.54-7.21) | 7.21 (6.88-7.54) | 0.193 |
| Average 7-day awake METs | 1.82(1.57-2.06) | 2.03 (1.79-2.28) | 0.318 |
| | African women (n=57) | Caucasian women (n=55) | P-value |
| Variable, Mean (\pm95% CI) | | | |
| Recorded days (Lost time excluded) | 6.92 (6.81-7.03) | 6.66 (6.55-6.77) | 0.003* |
| Average awake hours (24-hour cycle) | 17.38 (17.10-17.66) | 16.93 (16.65-17.21) | 0.036* |
| Average sleep hours (24-hour cycle) | 6.54 (6.27-6.81) | 7.09 (6.82-7.37) | 0.009* |
| Average 7-day awake METs | 1.84 (1.68-1.99) | 2.13 (1.97-2.28) | 0.015* |

* = Statistical significant ethnic differences ($p \leq 0.05$); Adjusted for confounders age and log γ -GT in African and Caucasian men & for BMI and log γ -GT in African and Caucasian women. Where MET refers to the Metabolic Equivalent of Task.

In Table 5.3, the average ICC-scores indicate the level of agreement for TEE within all 35 combinations of consecutive days (for example all two-day combinations: Mon-Tue, Tue-Wed, Wed-Thu, Thu-Fri, Fri-Sa and Sa-Sun), as well as the seven individual weekdays. All the ICC-scores showed values higher than 0.9. Even the average TEE of Sundays correlated strongly with the average TEE of Saturdays and Mondays in all ethnic and sex groups, and where Sundays formed part of the other combinations, high agreement was obtained between all the days within the combination (rho-square values ≥ 0.9). A variance components estimation indicated that differences across weekdays and within the combinations of consecutive days only contributed to 0.1% of the TEE variance observed. Participant differences explained 90.4% of the variance in TEE, whilst 9.5% of variance in data could not be explained by either daily differences or participant differences.

Table 5.3: Average TEE Intraclass correlation scores for combinations of consecutive days

| | Combinations of consecutive days for TEE | | | | | |
|------------------------|---|---------------|---------------|---------------|---------------|---------------|
| | 2 days | 3 days | 4 days | 5 days | 6 days | 7 days |
| African men | 0.968 | 0.977 | 0.981 | 0.977 | 0.986 | 0.988 |
| Caucasian men | 0.955 | 0.966 | 0.974 | 0.977 | 0.978 | 0.985 |
| African women | 0.933 | 0.950 | 0.960 | 0.967 | 0.972 | 0.976 |
| Caucasian women | 0.933 | 0.952 | 0.961 | 0.968 | 0.973 | 0.976 |

TEE = Total Energy Expenditure

Although the ICC-scores in table 5.3 indicated strong agreement between all weekdays and across the days within all the consecutive day combinations, the question still remained whether the average 24-h TEE of any weekday or combinations of consecutive days significantly differed from the weekly average TEE. Figure 5.2 visually displays the results of the dependent t-tests used to compare the weekly average TEE with the TEE of each day of the week (Figure 5.2a), as well as average TEE of all the 35 different combinations of consecutive days (Figure 5.2b-f) in all sex and ethnic groups. The TEE of African men, who were also the most sedentary group, indicated no significant deviations from the weekly average for any weekday (24-h cycle) or combinations of consecutive days. The greatest variations in average 24-h TEE (Figure 5.2a) were observed in Caucasian women, with the average TEE of Tuesday being significantly higher, and the average TEE of both Saturdays and Sundays significantly lower than the weekly average. The average TEE of Sundays was also significantly lower than the weekly average in Caucasian men. In the African women, however, the average TEE of Saturdays was significantly higher and Mondays significantly lower than the weekly average. Although not significant, the average TEE of Saturdays was higher than the weekly average in both the African and Caucasian men, and in the African men, the average TEE of Sundays even showed a higher value than the weekly average.

Figure 5.2 (b-f) illustrates the average TEE of different combinations of consecutive days in comparison with the weekly average TEE. If closely observing the average TEE in figure 5.2(a), Wednesday, Thursday and Friday were the only days not showing significant differences from the weekly average TEE in all ethnic and sex groups. The two consecutive combinations of these days (Figure 5.2b; Wednesday-to-Thursday and Thursday-to-Friday),

as well as the 3-day combination of these days (Figure 5.2c; Wednesday-to-Friday), also did not deviate significantly from the weekly average TEE.

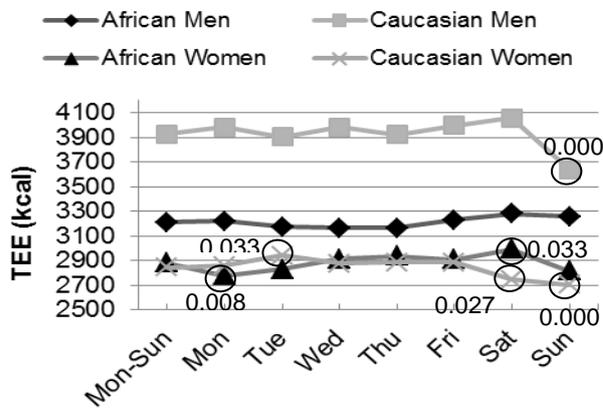


Fig. 2(a): Weekly average vs single weekdays

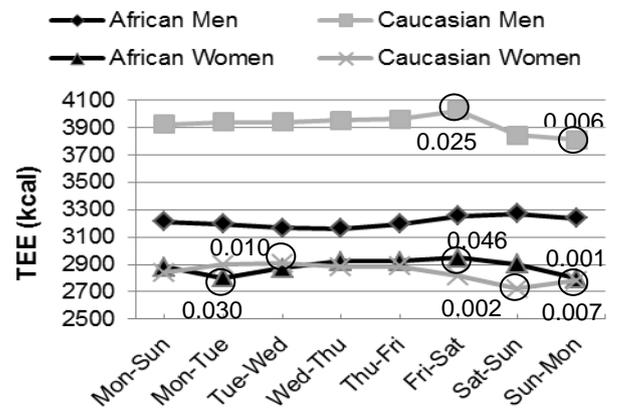


Fig. 2(b): Weekly average vs 2-day combinations

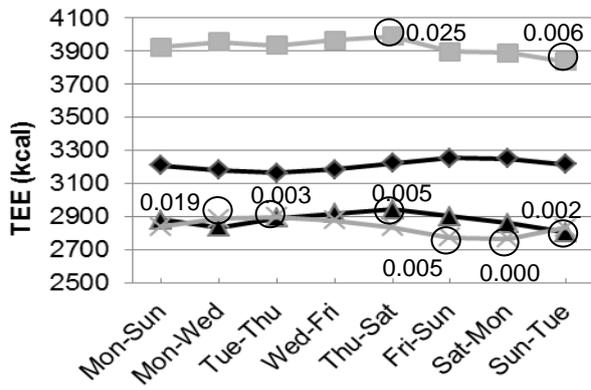


Fig. 2(c): Weekly average vs 3-day combinations

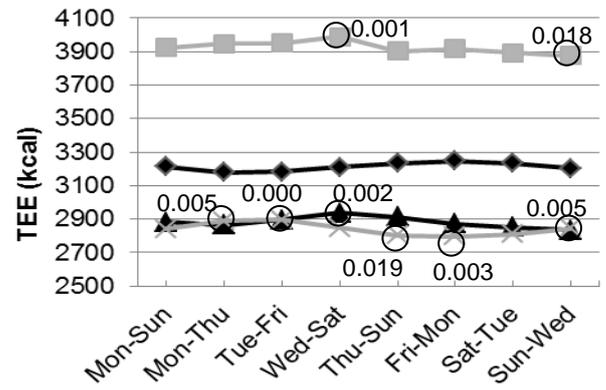


Fig. 2(d): Weekly average vs 4-day combinations

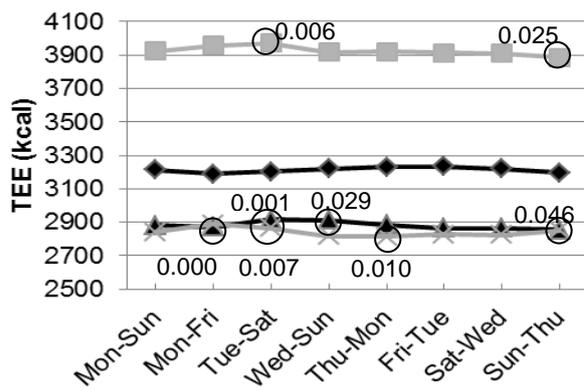


Fig. 2(e): Weekly Average vs 5-day combinations

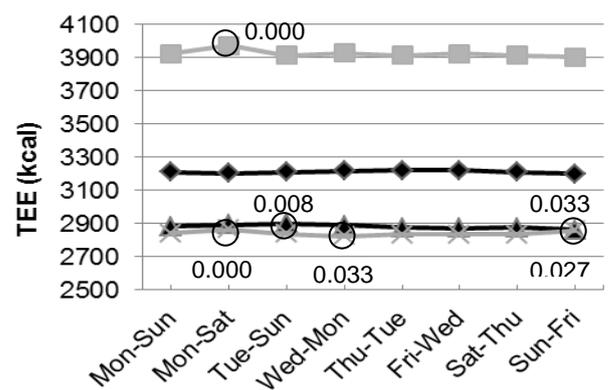
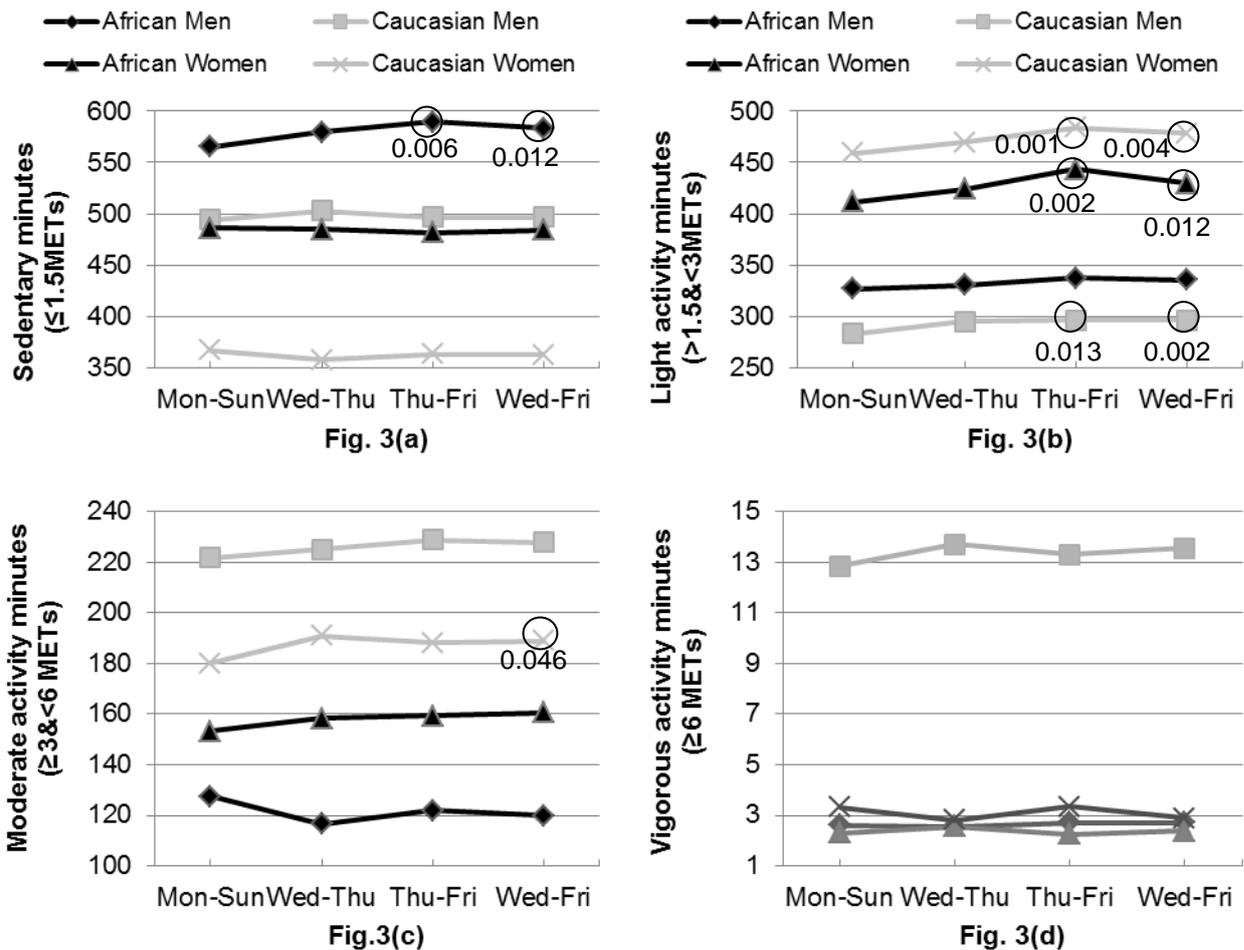


Fig. 2(f): Weekly average vs 6-day combinations

○ = Statistical significant difference from weekly average ($p \leq 0.05$)

Figure 5.2(a-f): Dependent t-test results comparing the weekly average TEE with all days of the week and different consecutive combinations of weekdays

As PA is observed during awake time, the Actiheart data for time asleep and time awake of the seven-day recording was separated in the current study. The average awake time spent in all the different MET-categories of the minimum consecutive day combinations (Wednesday-Thursday, Thursday-Friday and Wednesday-Friday) derived from the TEE-analyses (Figure 5.2) were then compared against the weekly average (Figure 5.3).



○ = Statistical significant difference from weekly average ($p \leq 0.05$)

Fig. 5.3(a-d): Dependent t-test results comparing average daily awake time spent in different MET-categories for selected combinations of consecutive days

Figure 5.3(a-d) above differs from the previous average TEE analyses (which included energy expenditure while asleep). Now, only the Wednesday-to-Thursday consecutive day combination did not indicate any significant deviation from the average weekly awake minutes spent in the four MET-categories in all ethnic and sex groups.

5.4 DISCUSSION

This study aimed to determine the minimum number of consecutive days the Actiheart device could be worn to reliably estimate EE and PA in an adult population of African and Caucasian South Africans. The main finding is that the two-day combination of Wednesday-to-Thursday showed the least deviation from the weekly average in all ethnic and sex groups. Therefore, this can be considered as a reliable consecutive day combination for estimating the average 24-h TEE, as well as awake time spent in the different MET-categories to describe habitual physical activity.

In a study investigating intra-individual variability and reliability in a seven-day exercise recording, it was suggested that the minimal number of days to reliably capture PA patterns is one week.⁵ The practicality of this was challenged in the current study, as the Actiheart data of 40% of the participants (143 of 359 participants) had to be excluded – either because the device was not worn for a full seven days, or due to long non-contact times, where the device failed. Data-reduction of this enormity has a major influence on statistical power in the quest to relate objectively measured PA to health related characteristics. Not only was the Actiheart recording of many participants in the current study disregarded due to inadequate wear time, but the researchers also had to provide some of the participants with a cortisone ointment after disconnection of the device due to inflamed and irritated skin. Wareham and colleagues also documented that the participant burden of a heart-rate monitor heightened after a wear period of four days due to skin irritation.²⁸

In the current study, the mixed model ICC-scores indicated high agreement of the average 24-h TEE across all individual weekdays, as well as across the days within all 35 consecutive day combinations for all the ethnic and sex groups - none of the scores being less than 0.9, indicating a high reliability. One could therefore argue that wearing the Actiheart on any weekday or for any consecutive day combination may provide a reliable estimate of EE and PA. However, the dependent t-test results clearly indicated that the average 24-h TEE of only Wednesday, Thursday and Friday, as well as the consecutive combinations of these three days (Wednesday-to-Thursday, Thursday-to-Friday and Wednesday-to-Friday) did not deviate significantly from the weekly average TEE. The latter therefore suggests a two-day or three-day combination of Wednesday, Thursday and Friday for reliable data. The clear agreement of these three days (individually and combined) with the weekly average is even

more noteworthy if one considers that in the current study the Actiheart recordings were obtained over a time frame of four months and in both sexes of two different ethnic groups (Africans and Caucasians). When only using data on waking time, the daily combinations which included Fridays were less consistent. However, the two-day combination of Wednesday-to-Thursday still did not significantly differ from the weekly average in all the ethnic and sex groups.

Although we are not aware of any similar studies using the Actiheart in an adult population, several studies have used pedometers and accelerometers to predict optimal wear time. A study by Tudor-Locke and co-workers indicated that the Wednesday, Thursday and Friday combination had the highest reliability ($r=0.942$) for estimating free-living EE in adults.²⁶ Three days of monitoring (any combination of days) were necessary to achieve a reliability of 0.80 when using pedometers and ActiGraphs in a large sample of adults with multiple sclerosis.²⁰ A Japanese study using the same device on an adult population indicated that any random three-day combination provides reliable estimates to predict weekly PA.¹⁶ Another pedometer study indicated that at least five consecutive days of wearing time were necessary to achieve average ICC-scores greater than 0.8.¹⁴ This study also commented that the average ICC-scores were larger within consecutive day combinations, compared to combinations of random days.

This study showed high amounts of daily time spent sedentary, as well as in light and moderate intensity activity for all sex and ethnic groups. If the energy expenditure of this study population is expressed in KJ/kg/day (kilojoules per kilogram per day) over a 24-h cycle (49.84 KJ/kg/day for African men, 66.03 KJ/kg/day for Caucasian men, 51.15 KJ/kg/day for African women and 64.75 KJ/kg/day for Caucasian women), the values of all the groups compare well with either the rural or urban dwellers in the Actiheart validation study done in Cameroon.⁴ Thus, the high amount of daily time spent in, for instance, moderate activity, could be explained by the occupation of the current study population, as teachers do a lot of walking during school hours and many (especially the Caucasian teachers) are involved in extracurricular activities (sport coaching and refereeing) after hours - the MET-value for slow walking (4.98 km/h) has previously been indicated as 3.3.¹¹ Also, the average daily awake time during the course of the week were 17 hours in all four groups, which is more recording hours than many accelerometer studies which usually regard twelve to fourteen hours per day as a valid recording.

Previous accelerometer studies defined a wear time of less than fourteen hours as being a valid day.^{9,13} After investigating the impact of accelerometer wear time on physical activity data outcomes, Herrmann and colleagues stated that wearing accelerometers for twelve hours or less per day, may underestimate time spent at various PA-levels. By increasing the accelerometer wear time, significantly more sedentary and light activity minutes were recorded when compared to minutes recorded in moderate intensity activity.¹⁴ In the current study, the average daily awake time in all the ethnic and sex groups was 17 hours with high recordings of sedentary, light and moderate activity time. Future researchers should therefore be cautious about implementing the minimum wear time of other instruments when using the Actiheart device, as this would hinder the reliable outcomes of time spent in different MET-categories.

5.5 SUMMARY

The results of this study suggest that the consecutive two-day combination of Wednesday and Thursday is adequate to reliably estimate EE for awake and sleep time combined, as well as PA during awake hours when using the Actiheart device in an urban adult population of South African school teachers. The inclusion of two ethnic groups (African and Caucasian), contributes to the reliability of this finding. The Wednesday-to-Thursday combination is not only a reliable estimate for weekly physical activity, but also provides practical convenience to the clinician, as well as the participant. The main advantage of this approach is reduction in the participant burden. Future research should test the reliability of the above-mentioned combination in other settings to work towards global standardization of Actiheart usage.

5.6 STUDY LIMITATIONS

Although this study provides valuable information, it is not without limitations. Individual calibrations (step testing) prior to fitting the Actiheart devices were not performed in this study due to the high clinical cardiovascular disease risk of many participants.¹⁸ Published research of Rennie and colleagues indicated that using heart-rate monitoring without individual calibration is reliable in medium-scale studies.²²

5.7 ACKNOWLEDGEMENTS

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CHAPTER 6

SUMMARY, CONCLUSION, LIMITATIONS AND RECOMMENDATIONS

- 6.1 SUMMARY
- 6.2 CONCLUSION
- 6.3 LIMITATIONS
- 6.4 RECOMMENDATIONS FOR FUTURE RESEARCH



6.1 SUMMARY

The main aim of the research presented in this thesis was to ascertain the associations between objectively measured physical activity (time spent in MET-categories), cardiovascular disease risk factors (ambulatory blood pressure, waist circumference), chronic stress (serum cortisol and GHQ total score) and leukocyte telomere length in a cohort of African and Caucasian school teachers.

Chapter 1 comprised the problem statement, study objectives and the proposed hypotheses. This chapter, as well as chapter 2, was written in accordance with the NWU guidelines. A literature review was provided in chapter 2 which focussed on the global and South African NCD risk, a thorough description of PA and its role in health enhancement, as well as biological links to disease and premature mortality, in other words, the involvement of chronic stress and physical inactivity in the augmentation of oxidative stress in the human body, telomere shortening and eventually disease.

CVD showed the greatest contribution to global NCD mortalities, with raised blood pressure as the leading risk factor and physical inactivity as one of the leading behavioural risk factors. Future projections indicate that ischaemic heart disease and NCD contributors will become greater mortality risks than communicable diseases in middle-income countries (such as South Africa). Almost half of the South African adult population are hypertensive, and more than half do not meet the recommended PA guidelines for health promotion.

Modern society is characterized by increased psychological stressors, high energy diets and physical inactivity that intensify allostatic load on the human body; increasing the risk of disease by for instance accelerated telomere shortening resulting in cell apoptosis. The buffering potential PA and exercise have on the cardiovascular- and cardiometabolic disease risk; chronic stress and premature mortality are well explained in literature. However, the PA dose-response relationship has mainly been investigated in western Caucasian populations, using self-report PA questionnaires. The protective potential of PA is therefore based on the participants' subjective interpretations of PA type and intensity. Questionnaires also have a limited ability to determine an individual's light-intensity activity, as well as daily time spent sedentarily. The use of objective tools to establish PA behaviour is becoming more common; however, researchers now fail to standardize the wear time of these devices. Studies using

objective measures for both PA and cardiovascular disease risk parameters to establish associations in different ethnic groups that included total daily awake time are scarce.

Only objective measures were used for the research presented in this thesis (the GHQ was only added for thoroughness on measures of cognitive perceived stress) and two ethnic groups (African and Caucasian) were included for analysis. This thesis is presented in article format and the three research articles (chapters 3-5) were written in accordance with the guidelines of the chosen journals for submission.

In chapter 3 (article 1), the association between seven-day objectively measured habitual PA and 24-h ambulatory blood pressure was assessed. This publication is unique in the sense that only the African and Caucasian participants with a full seven-day PA recording (Actiheart) were included and the true awake hours per 24-h cycle was used to determine the time spent in different MET-categories for associations with ambulatory blood pressure. The participants were all teachers and therefore more or less economically homogeneous – an advantage, as literature clearly indicates that economic status does influence PA behaviour. The hypertensive participants recorded 2.2 hours (12.4%) more daily awake sedentary time than normotensive participants and sedentary time was also a slightly better predictor of hypertension than moderate and vigorous activity time. Spending less daily awake time sedentary and more time doing light-intensity activities were beneficial for both the 24-h ambulatory SBP and DBP, regardless of race and sex. All the regression models revealed that a large waist circumference and high alcohol use significantly contributed to high blood pressure. Time spent doing light activities also showed a significant negative association with waist circumference - in other words, participants spending more time doing light-intensity activities presented with smaller waist circumferences. Participants with normal blood pressure and waist circumferences (below the ethnic and sex specific cut point), recorded less daily awake sedentary time and more time doing activities of light intensity than those with hypertension and large waist circumferences.

The aim of article 2 (chapter 4) was to determine the association between seven-day PA measures, chronic stress and leukocyte telomere length in the African and Caucasian teachers' cohort. The African population spent almost an hour more daily awake time sedentary, presented with slightly higher waist circumferences and had significantly higher 24-h SBP and DBP than the Caucasians. Although not the main focus of the study, it was

interesting to observe that this more clinically vulnerable African group had significantly shorter telomeres than the Caucasians, even after adjusted for age and log γ -GT (alcohol use) - a finding that is in contrast with literature. Shorter telomeres were associated with older age, increased alcohol consumption and higher central obesity. Time spent in the different MET-categories did not show any direct associations with either cortisol or leukocyte telomere length. Waist circumference did however indicate negative associations with both these parameters, as well as a strong positive correlation with the 24-h MAP in both ethnic groups. Time spent in light-intensity activity showed a significant negative association with waist circumference when assessing the group in total. It is therefore proposed that increasing daily time spent doing light-intensity activities could indirectly contribute to better health because of its beneficial effect on central obesity.

The participant burden of the Actiheart became clear during data collection and the recordings of 40% (n=143) of the SABPA II participants had to be disregarded either because the participants did not comply with the full seven-day wearing period or due to too many lost minutes during a 24-h recording cycle. The last article presented in this thesis (chapter 5) therefore aimed to determine the minimum number of consecutive days the Actiheart device could be worn to reliably estimate energy expenditure and habitual PA in an adult population. The intraclass correlation coefficient (ICC) scores indicated strong agreement between the 24-h TEE of all weekdays, as well as across the days within all 35 consecutive day combinations. However, the 24-h TEE of Wednesday, Thursday and Friday, as well as the combinations of these days (Wednesday-to-Thursday, Thursday-to-Friday and Wednesday-to-Friday) were the only days and daily combinations not indicating any significant differences from the weekly average TEE in all ethnic and sex groups. The average daily awake time spent in the different MET-categories for the above-mentioned combinations were then compared to the daily average of the seven-day recording. Now, only the Wednesday-to-Thursday combination did not differ significantly from the weekly average for all the MET-categories in all the ethnic and sex groups. This two-day combination (Wednesday-to-Thursday) was therefore proposed as a reliable Actiheart wear time that is practically convenient for the researchers and would certainly reduce the participant burden.

6.2 CONCLUSION

The conclusions drawn from this research project are presented in accordance with the hypotheses set in chapter 1.

Hypothesis 1:

Increased daily awake time spent in moderate and vigorous intensity habitual physical activities and decreased sedentary time will have a significant negative association with ambulatory blood pressure in a cohort of African and Caucasian teachers.

This hypothesis is partially accepted. Daily awake sedentary time proved to be a significant predictor for hypertension and the linear regressions indicated significant positive associations with both 24-h ambulatory SBP and DBP. Although daily time spent in both moderate and vigorous intensity activity showed significance as hypertension predictors, neither the partial correlations, nor the regressions revealed any relations of these two MET-categories with 24-h SBP and DBP. The use of an objective tool (the Actiheart) to measure PA enabled the researchers to accurately capture sedentary time, as well as activities of light intensity during daily awake hours. Both the partial correlations and the regression analyses indicated that increasing activities of light intensity (rather than the proposed moderate and vigorous intensity activities) significantly decreased ambulatory blood pressure.

Hypothesis 2:

African and Caucasian teachers who spent less daily awake time sedentarily and more daily awake time doing moderate to vigorous intensity habitual physical activities, will present with lower chronic stress levels and longer leukocyte telomere lengths.

This hypothesis is rejected, since none of the MET-category times indicated any significant associations with serum cortisol or telomere length. Shorter telomeres were associated with older age, increased alcohol consumption and higher central obesity. However, increasing light-intensity PA could lower age-related disease risk by contributing to a healthy waist circumference; which indicated significant associations with both the serum cortisol and telomere length. The significant negative association established between cortisol and waist circumference could indicate a possible cortisol down-regulation.

Hypothesis 3:

The Actiheart device should be worn for a minimum of two consecutive weekdays, along with both days of the weekend to reliably estimate energy expenditure and habitual physical activity behaviour in a cohort of African and Caucasian teachers.

This hypothesis is also rejected as combinations that included Saturdays and Sundays differed significantly from the weekly average for 24-h TEE. The two-day combination of Wednesday-to-Thursday was the only consecutive day combination that did not deviate significantly from the weekly average for both 24-h TEE (total energy expenditure), and as for daily awake time spent in any of the MET-categories (habitual PA) for all race and sex groups.

Seeking associations between habitual PA and selected physiological and biochemical parameters, the research in this manuscript again highlighted the importance of restricting daily sedentary time. The accumulation of light-activity time indicated to be beneficial by contributing to the maintenance of healthy ambulatory blood pressure and waist circumferences. A reason for the significant associations with light activity time could be the recording of habitual physical activity during true awake time – thoroughly capturing both sedentary time, as well as physical activities of light intensity. This is the first study according to the candidates knowledge that used true awake habitual physical activity time within a bi-ethnic group and the 17-hour average awake time surely contributed to the high amount of time spent in the different MET-categories (with the exception of vigorous activity). The finding in chapters 4 and 5 additionally indicated that a larger waist circumference and high alcohol use (serum γ -GT) significantly contribute to raised ambulatory blood pressure, as well as shorter telomeres. In summary, the results of this study recommend decreasing daily awake sedentary time by increasing activities of light intensity and to limit alcohol use. Lastly, the Wednesday-to-Thursday consecutive day combination seems to reliably estimate EE and habitual PA and could therefore be implemented in future studies with similar populations to help reduce the participant burden of the Actiheart.

6.3 LIMITATIONS

Although only objective measures were used for associations in the current study, some limitations do exist. The cross-sectional design of this project prevents causal links to be

inferred from the results. The thorough exclusion criteria used in all three publications (especially the exclusion of participants who did not comply with the instructed seven-day Actiheart wear time) negatively influenced the participant sample, weakening statistical power. This may have disguised the true protective potential of increased time spent in other MET-categories. Instead of individual calibration, a fitness level was chosen on the Actiheart programme after thorough oral questioning of a participant regarding his/her PA habits. This route was followed due to the high clinical CVD risk of many of the participants, as well as time constrictions of data collection within the multi-disciplinary project.

6.4 RECOMMENDATIONS FOR FUTURE RESEARCH

In order to improve the physical activity recommendations and consider the inclusion of sedentary time and activities of light intensity, it is strongly recommended that future research should use PA-questionnaires in combination with objective measures in various ethnic groups. The objective devices should preferably be worn for the full 24 hours in a selected time period and awake and sleep time separated. Standardizing PA questionnaires according to ethnicity, culture and education level is also recommended. Also, the Wednesday-to-Thursday consecutive day combination recommended by the current research should be tested in other populations to standardize Actiheart wear time. This would hopefully ensure larger sample sizes, as the participant burden of the objective devices would be lessened.

Furthermore, longitudinal evidence is needed to establish the true influence of lifestyle behaviours on physiological and biochemical parameters over time – especially to, for instance, test the theory of down-regulation of serum cortisol levels as a short-term protective mechanism of the body against development of disease. Intervention strategies could only be implemented if the pathological links of detrimental lifestyle behaviours are fully understood in various ethnicities.

APPENDICES

- APPENDIX 1: Ethical Approval
- APPENDIX 2: Informed Consent Form (SABPA II)
- APPENDIX 3: Guidelines for authors - Hypertension
- APPENDIX 4: Guidelines for authors - International Journal of Cardiology
- APPENDIX 5: Guidelines for authors - Journal of Physical Activity and Health
- APPENDIX 6: Language editor's declaration



APPENDIX 1
Ethical Approval



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Dear Dr Malan

6 February 2008

ETHICS APPROVAL OF PROJECT

The North-West University Ethics Committee (NWU-EC) hereby approves your project as indicated below. This implies that the NWU-EC grants its permission that, provided the special conditions specified below are met and pending any other authorisation that may be necessary, the project may be initiated, using the ethics number below.

| | |
|--|--|
| Project title: SABPA (Sympathetic activity and Ambulatory Blood Pressure in Africans) | |
| Ethics number: | N W U - 0 0 0 3 6 - 0 7 - S 6 |
| | <small>Institution Project Number Year Status</small> |
| | <small>Status: S = Submission, R = Re-Submission, P = Provisional Authorisation, A = Authorisation</small> |
| Approval date: 12 November 2007 | Expiry date: 11 November 2012 |

Special conditions of the approval (if any): None

| |
|---|
| <p>General conditions:</p> <p><i>While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:</i></p> <ul style="list-style-type: none"> • The project leader (principle investigator) must report in the prescribed format to the NWU-EC: <ul style="list-style-type: none"> - annually (or as otherwise requested) on the progress of the project, - without any delay in case of any adverse event (or any matter that interrupts sound ethical principles) during the course of the project. • The approval applies strictly to the protocol as stipulated in the application form. Would any changes to the protocol be deemed necessary during the course of the project, the project leader must apply for approval of these changes at the NWU-EC. Would there be deviated from the project protocol without the necessary approval of such changes, the ethics approval is immediately and automatically forfeited. • The date of approval indicates the first date that the project may be started. Would the project have to continue after the expiry date, a new application must be made to the NWU-EC and new approval received before or on the expiry date. • In the interest of ethical responsibility the NWU-EC retains the right to: <ul style="list-style-type: none"> - request access to any information or data at any time during the course or after completion of the project; - withdraw or postpone approval if: <ul style="list-style-type: none"> · any unethical principles or practices of the project are revealed or suspected, · it becomes apparent that any relevant information was withheld from the NWU-EC or that information has been false or misrepresented, · the required annual report and reporting of adverse events was not done timely and accurately, · new institutional rules, national legislation or international conventions deem it necessary. |
|---|

The Ethics Committee would like to remain at your service as scientist and researcher, and wishes you well with your project. Please do not hesitate to contact the Ethics Committee for any further enquiries or requests for assistance.

Yours sincerely

Prof M M J Lowes
(chair NWU Ethics Committee)

APPENDIX 2
Informed consent form (SABPA II)



PARTICIPANT INFORMATION AND CONSENT FORM (SABPA II)

**NORTH-WEST UNIVERSITY
POTCHEFSTROOM CAMPUS
SCHOOL FOR PHYSIOLOGY, NUTRITION AND CONSUMER SCIENCES**

PART 1

PRINCIPAL RESEARCHER: Prof Leoné Malan, Subject Group Physiology

PROJECT LEADER: Prof Leoné Malan

Associate Researcher(s): The postdoctoral fellows involved in this trial are Dr. P Szabolcs, Mr M Glynn. Other persons assisting in the study are Professors Nico T Malan, Alta E Schutte, Hugo W. Huisman, Johannes M. van Rooyen, Rudolph Schutte, Drs. Carla M.T. Fourie, Wayne Smith, Carina Mels, Mrs Tina Scholtz, Lisa Uys, Mr Ruan Kruger (Hypertension in Africa Research Team), Proff. Hans de Ridder (Anthropometry, Physical activity), Johan Potgieter, Dr Tumi Khumalo (Psychology), Professors Linda Brand and Brian Harvey (Pharmacology), Kobus Mentz (Education), Francois van der Westhuizen (Biochemistry), Ronel Pretorius (Nursing), Yackoob Seedat (Kwazulu Natal), Paul Rheeder (Pretoria University), Proff Nancy Frasure-Smith and Francois Lespérance (Canada), Drs Alaa Alkerwi (Luxembourg), M Hamer (UK), Manja Reimann, Proff Tjalf Ziemssen, C Kirschbaum (Germany), Eco JCN de Geus (Netherlands); Markus Schlaich & Dr G Lambert (Australia), Prof Morten Rostrup (Norway).

This Participant Information and Consent Form is **8** pages long. Please make sure you have all the pages.

Your Consent

You are invited to take part voluntarily in this research project.

This participant information document contains detailed information about the research project which has been explained to you verbally. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part.

Please read this *Participant Information Form* carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project. You will be given a copy of the Participant Information and Consent Form to keep as a record.

What is the study about?

The aim of this project is to have an impact on the eventual prevention and treatment of lifestyle diseases in Africans from South Africa. New knowledge regarding the relationship between higher nervous system activity implicating cardiovascular, metabolic and psychological well-being will improve understanding and change strategies at the roots of treatment and prevention of lifestyle diseases.

Our research has shown that lifestyle diseases in urban Africans present higher obesity levels, high blood pressure or hypertension prevalence rates and the experiencing of more stress. This pattern is enhanced during psychosocial stress/urbanisation in participants with a specific coping style. Hence, the planned SABPA project, which is the first study in South Africa where coping and direct markers of in Africans will be measured.

Purpose of study

The purpose of this study is to *repeat most of our previous measurements* although not the stressor exposure measures. We will investigate biological markers associated with higher nervous system activity in urban teachers with a specific coping style.

To investigate the relationship between blood pressure, inflammation, obesity, stress and coping in more detail we are going to perform this study in 409 men and women from the North-West province, aged 25-65 years. A comprehensive assessment of the cardiovascular and nervous systems by means of non-invasive painless techniques will be performed and blood and saliva samples will be taken by an experienced research nurse to determine your blood sugar, cardiovascular, inflammation and stress hormone levels amongst other health markers.

Procedures

All measurements are performed in the Metabolic Unit (Lipid Clinic) of the University. A researcher has explained the entire procedure in detail and while you are reading this information document you have time to ask questions and to have clarified matters. If you are fine with the explained procedure you are requested to sign a *consent form (at the end of this document). Remember all personal data will be handled with care and remain confidential.

**By consenting to participate in this study, you consent to the storage and later analysis and testing of your stored blood samples for the purposes noted above. Your blood will also be tested for preliminary results on HIV status, since your HIV status may directly influence the*

main purposes of this study. If you would like to know what your HIV-status is, we will provide it. If tested positive we will refer you to your doctor and he/she will perform the necessary tests which will allow you to apply for chronic medication benefits. Also, the blood cells from your donated blood sample will be used to investigate the molecular genetics of higher nervous system activity and Type 2 diabetes in order to enable pre-symptomatic diagnosis of hypertension and diabetes in the long term.

Why was I chosen? Educators are exposed to changing curricula and disciplinary problems whilst living in an urban environment adding to higher stress experiencing and nervous system activity.

How was I chosen?

Inclusion criteria:

All SABPA I (2008/2009) black (Phase I) and Caucasian (Phase II) teachers (male and female)

Exclusion criteria: *pregnancy, lactation, temperature >37°C. You cannot be included if you have donated blood or been vaccinated in the previous 3 months.*

What will be expected of me?

You, as participant will be screened once by a registered nurse to be eligible complying with the inclusion criteria. The following procedures will be followed:

- Recruitment and informed sessions with all participants will be done two months prior to the study (October - November 2010, Phase I, and **November, 2011, Phase II**) and informed consent forms will be signed.
- After selection of all participants, the details of the project will be discussed with you in English or your home language, i.e. what the exact objectives of the study are, what procedures will be taken and what will be expected from each of you (e.g. overnight stay, resting blood pressure procedures and fasting urine and blood samples are required, importance of complying with the correct sampling methods, incentives). You will be given the opportunity to ask questions.
- Data collection for each participant will involve two days (15 min in the morning and 2½ hours in the evening) on Day I; and 2 hours on Day II):

DAY I

- On day I between 07:00-08:00, the blood pressure apparatus, which will measure your blood pressure and heart function, will be applied to your arm and waist at your school and you can then resume your normal daily activities.
- Urine sampling (24h) and 24h diets will commence.
- At the end of Day I (**15:00**) you have to visit us or be transported from your schools to the Physiology F12 building (NWU) and will overnight in the Metabolic Unit Research Facility of the North-West University. This unit is a research unit for human studies and equipped with 10 well-furnished bedrooms, a kitchen, two bathrooms and a television room. Each of you will be subjected to the following procedures:
 - At 15:00 you will be welcomed at F12 at the HART clinic and eye measurements including saliva sampling pertaining to cardiometabolic health will commence.
 - Hair sampling and pre-counselling for HIV/AIDS will be done.
 - You will go then go the Metabolic Unit Research Facility of the North-West University (G17) to receive your own bedroom. All other apparatus will be shown and the procedures, which will be done, will be explained again and you will receive dinner.
 - After dinner, the psychosocial questionnaires will be completed under supervision of registered clinical psychologists/postgraduate students. Completion of questionnaires will take approximately 40 min, From 22:00 you will be fasting, therefore, this will be you last meal for Day I as you must be fasting on Day II for obtaining good results.
 - Thereafter, you can relax and watch television or socialize with your co-participants. It will be wise to go to bed not later than 22:00 as the blood pressure apparatus will take measurements every hour during the night and it can be tiring.

DAY II

- At 06:45 on Day II in the anthropometric station your weight, height and body circumferences will be measured.
- Urine sampling will be completed before 07:30 after which the blood pressure apparatus will be removed (07:30 after last measurement).
- Next the cardiovascular measurements will follow consisting of three separate procedures:
 - Firstly, after being in semi-recumbent position for 10 minutes your blood pressure will be taken in duplicate with the sphygmomanometer (the same as used at clinics) with a resting period of 5 minutes in between.
 - Secondly, our registered research nurse will measure the ECG which measures heart function, with 12 leads, which will be placed into position on your rib cage/front part of the body.
 - Thirdly, the assessment of pulse wave velocity will follow, i.e. giving an indication of how stiff your vessel walls are. The stiffer your vessel wall is the

faster the blood travels from one point of your body to another. These painless measurements will require two technicians using blunt probes (tonometer) putting light pressure on the neck and on the foot to measure the velocity of the pulse waves. This takes only a few minutes.

- A once-off blood sample of 48 ml will be obtained between 08:30 - 09:00 from a vein in your dominant arm.
 - Lastly, an ultrasound device will be taken of your arteries in the neck with a blunt probe to indicate the intrinsic thickness of your arteries which contributes to high blood pressure.
 - You have reached the end of the sampling phase.
- Immediate feedback on your HIV/AIDS status, obesity levels, blood pressure and blood glucose/sugar values will be given. *HIV/AIDS post-test counselling will be arranged if you are tested positive.*
- **Thank you for your participation! You now will have the opportunity to shower and a take-away breakfast will be given.**
- You will now be transported back to your school and after one week you will receive your 24-hour blood pressure, 12 lead ECG and eye reports as well as sleeping disturbances/sleep apnoea risk.

Possible Risks

The measurements performed in our study will include only non-invasive techniques that are not expected to reveal any risks but might cause little discomfort. The taking of blood samples is an invasive procedure with a minimal risk of bleeding. Thus the procedure may cause only a few seconds of light discomfort. All tests will be performed by experienced research nurses of our department. There may be additional unforeseen or unknown risks.

Precautions to protect the participant

The Metabolic Unit facility of the NWU is fully equipped, and in case of an emergency which could not be handled by the registered nurse, the supervising medical doctor P de K Geldenhuys will be contacted. Dr. Geldenhuys was notified before the study commenced that this study would be taking place, and that there was a slight possibility that he might be contacted. Supporting medical treatment care facilities will be at hand anytime if needed.

Other Treatments Whilst on Study

It is important to tell the research staff about any treatments or medications you may be taking, including non-prescription medications, vitamins or herbal remedies during your participation in the study.

Incentives

1. All teachers will receive feedback on their health profile and if necessary references will be given to physicians/clinics/hospitals.
2. Blood pressure, kidney functioning, eye measures and ECG monitoring (normally costing R8000.00). Your benefit of participation is a comprehensive assessment of the cardiovascular and metabolic condition including investigation of blood pressure, inflammatory status and psychological well-being. These examinations will help us to assess the degree of vascular impairment of the arteries and to predict your risk of possible cardiovascular events such as heart attacks and stroke. The results may assist your doctor in decision making for further treatment or for instituting preventive measures. Our study will also contribute to the identification of possible factors leading to high blood pressure. As 24-hour ambulatory blood pressure monitoring is required for the diagnosis of hypertension, medical aids insist on this method of diagnosis to qualify for chronic medication. Additional testing could also reveal illnesses of a chronic nature and would serve as a motivation to qualify for chronic medication, such as metabolic syndrome, anti-inflammatory and cholesterol-lowering drugs.
3. Monetary incentive as compensation for discomfort and token of appreciation of R100.00 / US\$±14
4. Diet for 24 hours (R150.00 / Two breakfasts, lunch and dinner

Privacy, Confidentiality and Disclosure of Information

By consenting to participate in this study, you consent to the storage and later analysis and testing of your stored blood samples for purposes noted above. Your blood samples will be discarded immediately after analysis. All information provided by you and the results of tests will be treated in the strictest confidence, and will only be used for the purpose of this research project. It will only be disclosed with your permission, except as required by law. The results of your medical tests will be labelled only with a code number, and will be stored separately from any identifying information. When the results are analysed we will be looking for differences between groups of people, not at the results of individuals. No information that could identify any person taking part in the study will be revealed when the results are reported.

Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the North-West University.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw.

Ethical Guidelines

This project will be carried out according to Ethical Guidelines of the Helsinki declaration from 2008, with additional notes in 2002. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of *North-West University Potchefstroom: (NEW-EC): 0003603S6*

Further Information or Any Problems

If you require further information or if you have any problems concerning this project, you can contact the principal researcher or *the other* researchers responsible for this project.

Project Leader: Prof Leoné Malan (018-299 2438); Cell 0733765321

A handwritten signature in black ink, appearing to read 'L Malan', is centered within a light gray rectangular box.

Signature

PART 2

To the subject signing the consent as in part 3 of this document

You are invited to participate in a research project as described in paragraph 2 of Part 1 of this document. It is important that you read/listen to and understand the following general principles, which apply to all participants in our research project:

- 1. Participation in this project is voluntary.**
- 2. It is possible that you personally will not derive any benefit from participation in this project, although the knowledge obtained from the results may be beneficial to other people.**
- 3. You will be free to withdraw from the project at any stage without having to explain the reasons for your withdrawal. However, we would like to request that you should rather not withdraw without a thorough consideration of your decision, since it may have an effect on the statistical reliability of the results of the project.**
- 4. The nature of the project, possible risk factors, factors which may cause discomfort, the expected benefits to the subjects and the known and the most probable permanent consequences which may follow from your participation in this project, are discussed in Part 1 of this document.**
- 5. We encourage you to ask questions at any stage about the project and procedures to the project leader or the personnel, who will readily give more information. They will discuss all procedures with you.**

PART 3

Consent

Title of the project: “**THE SABPA STUDY** (Sympathetic activity and Ambulatory Blood Pressure in Africans)”.

I, the undersigned..... (full names) read /
listened to the information on the project in PART 1 and PART 2 of this document and I
declare that I understand the information. I had the opportunity to discuss aspects of the
project with the project leader and I declare that I participate in the project as a volunteer. I
hereby give my consent to be a subject in this project.

(Signature of the subject)

Signed at on2011/12

Witnesses

1.

2.

Signed at on20011/12

APPENDIX 3
Guidelines: Hypertension

GENERAL INSTRUCTIONS FOR PREPARING A MANUSCRIPT

TITLE PAGE (Page 1, but do not number)

- Full title of manuscript, in capital letters, limited to 120 characters total.
- Authors' full names and affiliations
- A short title (total characters must not exceed 50, including spaces) to be typeset at the top of the journal page
- Word count of manuscript, including references, figures, legends, word count of abstract, and total number of figures
- The full name, title, and complete address for corresponding author, including street and post office box as well as telephone and fax numbers, and email address

ABSTRACT

- Maximum abstract length is 250 words
- Do not use acronyms or abbreviations
- Do not use subheadings
- Do not cite references
- The abstract should include the rationale for the study, a brief description of methods and presentation of significant results, and a succinct interpretation of the data.
- Provide five to seven key words for your manuscript, using Index Medicus as a guide

TEXT

Abbreviations

Abbreviations should be defined at the first mention in the text.

Methods

- The methods section should provide sufficient detail for the experiments to be reproduced.

- **Materials and Data Availability:**
- To allow others to replicate and build on work published in *Hypertension*, authors should make materials, data, and associated protocols available to readers or list the primary source of materials. Authors must disclose upon submission of the manuscript any restrictions on the availability of materials or information.
- Authors should make Unique Materials (e.g., cloned DNAs; antibodies; bacterial or animal cells; viruses; and computer programs) promptly available on request by qualified researchers for their own use. It is reasonable for authors to charge a modest amount to cover the cost of preparing and shipping the requested material and some materials may require a Materials Transfer Agreement between institutions.
- **Studies in Humans:** Indicate that the study was approved by an institutional review committee and that the subjects gave informed consent. All studies that involve the use of humans must adhere to the principles of the Declaration of Helsinki and Title 45, U.S. Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. Describe the characteristics of human subjects or patients and indicate that the procedures followed were in accordance with institutional guidelines.
- **Blood Pressure Methods for Human Studies:** Blood pressure measurement methods should be described in detail in the text or by reference. Information should include number of readings, instrument type(s), cuff size(s), arm position, posture, and observer training.
- **Statistics:** A subsection on statistics should be included in the Methods section and the measures of variance, such as standard deviation or standard error, should be indicated.
- Methods should be limited to essential new information. To save space for the authors and the journal, if methods have been previously published, the author may refer to that paper and submit copies of that paper as reference material.
- The following information should be included as an **Online Data Supplement**:
 - For animals used in experiments, state the species, strain, number used, and other pertinent descriptive characteristics.
 - For human subjects or patients, describe their characteristics.
 - When describing surgical procedures on animals, identify the pre-anesthetic and anesthetic agents used and state the amount or concentration and the route and frequency of administration for each. The use of paralytic agents, such as curare or

succinylcholine, is not an acceptable substitute for anesthetics. For other invasive procedures on animals, report the analgesic or tranquilizing drugs used. If none was used, provide justification for such exclusion. Generic names of drugs must be given.

- Manuscripts that describe studies on humans must indicate that the study was approved by an institutional review committee and that the subjects gave informed consent. Reports of studies on both animals and humans must indicate that the procedures followed were in accordance with institutional guidelines. To save space for the authors and the journal, if methods have been previously published, the author may refer to that paper and submit copies of that paper as reference material.

Discussion

This section should not be used to restate the results but rather to illuminate and place into perspective the results. Excessive discussion and reiteration of points that are obvious from the results are discouraged.

Perspectives

Authors should include a brief (fewer than 250 words) "Perspectives" section at the end of the Discussion Section. The "Perspectives" section should be clearly labeled with a separate heading. The purpose of "Perspectives" is to indicate the broad implications of the study, and to permit reasonable speculation on the overall importance and future directions of the work. Such perspectives should not replace the conclusions drawn from the study and should be limited to one paragraph. This section should, however, replace the "In summary..." paragraph that is often placed at the end of the discussion.

Acknowledgments

The Acknowledgments section lists substantive contributions of individuals.

Sources of Funding

Authors **must** list all sources of support for research in this section.

Conflict(s) of Interest/Disclosure(s) Statement

Authors **must** disclose any and all relationships that could be perceived as real or apparent conflict(s) of interest as a **FOOTNOTE** after the Sources of Funding section. Conflict-of-

interest/disclosure will be published as a footnote to the accepted article. This pertains to relationships with pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the article. Such relationships include, but are not limited to, employment by an industrial concern, ownership of stock, membership on a standing advisory council or committee, being on the board of directors, or being publicly associated with the company or its products. Other areas of real or perceived conflict of interest related to the subject of the article could include receiving honoraria or consulting fees or receiving grants or funds from such corporations or individuals representing such corporations.

If no author has anything to disclose, please list "None".

Figures

Figures must conform to the journal's style -- Detailed guidelines and examples are available at [Figure Instructions](#).

References

References must conform to the journal's style -- For style, consult the [American Medical Association Manual of Style, 9th ed](#), Baltimore, MD, Williams & Wilkins, 1998. (NOTE: The use of et al. in the author listing of references is allowed only when the author list exceeds 15 authors.).



APPENDIX 4

Guidelines: International Journal of Cardiology

INTERNATIONAL JOURNAL OF CARDIOLOGY

Affiliated with the International Society for Adult Congenital Heart Disease

AUTHOR INFORMATION PACK

DESCRIPTION

The *International Journal of Cardiology* is devoted to **cardiology** in the broadest sense. Both basic research and clinical papers can be submitted. The journal serves the interest of both practicing clinicians and research workers. Editorials, Brief Reports and Review Articles covering recent developments are included. Controversial techniques, issues on health policy and social medicine are discussed and serve as useful tools for encouraging debate. *International Journal of Cardiology* has no page charges.

GUIDE FOR AUTHORS

Introduction

The International Journal of Cardiology is a global journal of cardiology, cardio-metabolic and vascular sciences. Articles reporting clinical observations and interventions, experimental studies and theoretical concepts are all welcome provided they are of major scientific importance and clinical relevance. The journal covers all aspects of cardiology from genes to populations. The journal commissions high quality review articles from distinguished authors; unsolicited reviews will also be considered and will be subject to peer review. Letters to the editor are welcome. Case reports can only be considered if formatted as a letter. Submission of a manuscript to this journal gives the publisher the right to publish that paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

TYPES OF MANUSCRIPTS

The journal invites Original Articles, Reviews, Editorials and Letters to the Editor. Case Reports will be considered only in the form of Letters to the Editor. Please follow the instructions relevant to type of manuscript being submitted. If the article to be submitted reports a randomized trial the authors are requested to consult the CONSORT (Consolidated Standards of Reporting Trials) Statement (see web link www.consort-statement.org) for advice on specific features of the trial to report on in the manuscript.

ORIGINAL ARTICLES

Original Articles should report original research not previously published or being considered for publication elsewhere, meeting high standards of scientific integrity. There is no maximum word count.

The standard layout is given below:

Layout Of Original Articles Divide the manuscript into the following sections: Title page, Structured Abstract, Key words (3-6), Introduction, Methods, Results, Discussion, Acknowledgments, References. The editors will consider the use of other sections if more suitable for certain manuscripts. Type double-spaced.

The Title Page should include: **1.** The title (not to exceed 25 words) **2.** The full list of authors and for each author a numbered footnote. The footnote should state the author's academic affiliation and the following statement of authorship: "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation". Any author unable to make this statement must instead state their specific contribution to the manuscript. **3.** Corresponding author and contact details **4.** Acknowledgement of grant support **5.** Any potential conflicts of interest, including related consultancies, shareholdings and funding grants

The Next Page Should Include:

A **Structured Abstract**, of no more than **250 words**. As this may be the only part of the article read by some readers it must include sufficient detail for an adequate summary of the whole manuscript. The preferred subheadings are ***Background, Methods, Results and Conclusions***, although a merged Methods and Results subheading is also permitted if this permits more economical expression. A list of up to 6 keywords.

The Next Page should commence the main article subdivided into the following sections:

The Introduction should be brief and set out why the study has been performed along with a review of relevant previous work only where essential.

The Methods should be sufficiently detailed so that readers and reviewers can understand precisely what has been done. Standard methods can be referenced. Manuscripts reporting data obtained from research conducted in human subjects must include a statement of assurance in the Methods section of the manuscript that (1) informed consent was obtained

from each patient and (2) the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Manuscripts reporting experiments using animals must include a statement giving assurance that all animals received humane care and that study protocols comply with the institution's guidelines. A Statistical Methods Section must be included where relevant. This should include the statistical methods used with sufficient clarity for the findings to be reproduced by independent analysis of the dataset, a statement on how the data presented were selected including prospective sample size calculations, the reasons for including/excluding subjects or data points, and what steps the authors have taken, if any, to exclude intentional or unintentional bias in recruitment, measurement, data retention, analysis, reporting and comment.

The Results should be presented precisely. Keep discussion of their importance to a minimum in this section of the manuscript. Present 95% confidence intervals with p values. When describing normal distributions, denote the standard deviation explicitly, e.g. with the abbreviation SD, rather than a \pm sign. When describing uncertainty of a mean, denote the standard error of the mean explicitly, e.g. with the abbreviation SEM, rather than a \pm sign. It is a condition of final acceptance of manuscripts, for the purpose of scientific integrity, that for each figure, raw numerical values should be uploaded in an Online Data Supplement. These supplement files should be one or more standard spread sheet files. Raw x and y values for all scatterplots should be given. For bar charts and histograms, underlying raw values and categories should be given. For each Kaplan-Meier survival curve, for each patient a time-to-event-or-censoring and censor status should be given. Authors may additionally optionally upload comprehensive numerical datasets of the study.

The Discussion should directly relate to the study being reported rather than a general review of the topic.

A Study limitations subsection must be included and should disclose any reasons the findings may not be applicable more broadly.

Conclusions should be limited to a brief summary and the implications of the data presented.

References Discoverability of research and high quality peer review are ensured by online links to the sources cited. In order to allow us to create links within ScienceDirect and to abstracting and indexing services, such as Scopus, CrossRef or PubMed, please ensure that

data provided in the references are correct. Please note that incorrect surnames, journal/book titles, publication year and pagination may prevent the link creation. When copying references, please be careful as they may already contain an error. There are no strict requirements on reference formatting at submission. **References can be in any style or format as long as the style is consistent.** *Author(s) name(s), journal title/book title, chapter title/article title, year of publication, volume and issue/book chapter and the pagination must be present.* The reference style used by the journal will be applied to the accepted article by Elsevier at the proof stage. Note that incorrect or missing data will be highlighted at proof stage for the author to correct. The reference style used by this journal is Vancouver Numbered. If you do wish to format the references yourself they should be arranged according to the following examples Examples: [1] De Soyza N, Thenabadu PN, Murphy ML, Kane JJ, Doherty JE. Ventricular arrhythmia before and after aortocoronary bypass surgery. *Int J Cardiol* 1981; 1:123-130. [2] Akutsu T. Artificial heart: total replacement and partial support. Amsterdam: Elsevier/North-Holland, 1975. [3] Goldman RH. Digitalis toxicity. In: Bristow MR, editors. *Drug-induced heart disease*. Amsterdam: Elsevier/North-Holland, 1980:217-40. **Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al.** Do not include references to personal communications, unpublished data or manuscripts either "in preparation" or "submitted for publication". If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against reference list after your manuscript has been revised.

Personal and member subscribers can access the journal online via:

<http://www.internationaljournalofcardiology.com>.

Institutional subscribers can access the journal online via ScienceDirect. For more information, please go to: <http://www.sciencedirect.com>.



Appendix 5
Guidelines: Journal of Physical Activity and Health

JPAH is a peer-reviewed journal. Manuscripts reporting Original Research, Public Health Practice, Technical Notes, Brief Reports, or Reviews will be reviewed by at least two reviewers with expertise in the topical field, and the review process usually takes from 6 to 8 weeks. A double-blind method is used for the review process, meaning authors and reviewers remain unknown to each other. All types of manuscripts submitted to *JPAH* are judged on the following primary criteria: adherence to accepted scientific principles and methods, the significant or novel contribution to research or practice in the field of physical activity, clarity and conciseness of writing, and interest to the readership. There are no page charges to contributors.

Manuscripts generally should not exceed 25 pages (~5000 words including everything *except* title and abstract pages). Reviews should not exceed a total of 30 pages and Brief Reports should not exceed 15 pages. Major exceptions to these criteria must be approved through the Editorial Office before submission. Submissions should not include more than 10 tables/graphics, and should follow the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (visit www.icmje.org/index.html for more detail). *JPAH* welcomes and encourages the submission of supplementary materials to be included with the article. These files are placed online and can be accessed from the *JPAH* website. Supplemental material can include relevant appendices, tables, details of the methods (e.g., survey instruments), or images. Contact the Editorial Office for approval of any supplemental materials.

Standardized Publication Reporting Guides

JPAH highly recommends that authors refer to relevant published reporting guidelines for different types of research studies. Examples of reporting guidelines include:

1. Consolidated Standards of Reporting Trials (CONSORT) - www.consort-statement.org/
2. Meta-analysis of Observational Studies in Epidemiology (MOOSE) - www.consort-statement.org/mod_product/uploads/MOOSE%20Statement%202000.pdf
3. Quality of Reporting of Meta-analyses (QUOROM) - www.consort-statement.org/mod_product/uploads/QUOROM%20Statement%201999.pdf
4. Strengthening the Reporting of Observational studies in Epidemiology (STROBE) - www.strobe-statement.org/
5. Improving the Quality of Web Surveys: The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) - www.jmir.org/2004/3/e34/

Manuscripts must be electronically submitted to mc.manuscriptcentral.com/hk_jpah in Microsoft Word® (*.doc) or rich text (*.rtf) format *only*. Do *not* submit a .pdf file. Graphics should be submitted in .tif or .jpg formats only. Before submitting, authors should complete the Manuscript Submission Checklist (see below). Authors may be asked to provide Human Kinetics with photo-ready graphics and/or hard copy of the text. Authors are responsible for confirming the accuracy of the final copy, particularly the accuracy of references, and to retain a duplicate copy to guard against loss. Final review of the pre-published text is the responsibility of the authors. Authors of manuscripts accepted for publication must transfer copyright to Human Kinetics as applicable.

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Title page: The manuscript must include a title page that provides the full title, a brief running head, manuscript type (see definitions below), three to five key words not used in the title of the manuscript, abstract word count, manuscript word count (inclusive of all pages except the abstract and title page), and date of manuscript submission. *Do not include author names on the title page*. The order of submission must be 1) Title page, 2) Abstract, 3) Text, 4) Acknowledgments, 5) Funding source, 6) References, 7) Tables, 8) Figures/Graphics.

Manuscript types

Original Research: A manuscript describing the methods and results of a research study (quantitative or qualitative), including the background and purpose of the study, a detailed description of the research design and methods, clear and comprehensive presentation of results, and discussion of the salient findings.

Public Health Practice: A manuscript describing the development or evaluation of a public health intervention to increase or promote physical activity in a community setting, or a study that describes translation of research to practice.

Technical Note: A short article that presents results related to a new or modified method or instrument related to physical activity measurement or an important experimental observation.

Brief Reports: A short article (15 or fewer pages), usually presenting the preliminary or novel results of an original research study or public health practice program.

Reviews: Manuscripts that succinctly review the scientific literature on a specific topic. Traditional narrative reviews are discouraged. However, well-conducted systematic reviews and meta-analyses are highly encouraged. The Editorial Office may recruit reviews on specific topics. All review articles must have approval from the Editorial Office prior to submission.

Manuscript sections

Abstract: All manuscripts must have a structured abstract of no more than 200 words. Required headings are 1) Background, 2) Methods, 3) Results, and 4) Conclusions.

Text: The entire manuscript must be double-spaced, including the abstract, references, and tables. Line numbers must appear on each page in the left margin. A brief running head is to be included on the upper right corner of each page; page numbers must appear on the bottom right corner of each page.

For studies involving human subjects, the Methods section must include a statement regarding institutional approval of the protocol and obtaining informed consent.

References: For reference lists, authors must follow the guidelines found in the *American Medical Association Manual of Style: A Guide for Authors and Editors* (10th ed.). Examples of reference style:

Journal Articles: Surname of first author, initials, then surname and initials of each co-author; title of article (capitalize only the first word and proper nouns), name of the journal (italicized and abbreviated according to style of Index Medicus), year, volume, and inclusive page numbers.

Melby CL, Osterberg K, Resch A, Davy B, Johnson S, Davy K. Effect of carbohydrate ingestion during exercise on post-exercise substrate oxidation and energy intake. *Int J Sport*

Nutr Exerc Metab. 2002;12:294–309.

Book References: Author(s) as above, title of book (italicized and all major words capitalized), city and state/province of publication, publisher, and year.

Pearl AJ. *The Female Athlete*. Champaign, Ill: Human Kinetics; 1993.

Chapter in an Edited Book. Same as book references, but add the name of the chapter author(s) and title of chapter (capitalize first word and proper nouns) before the book information and inclusive page numbers.

Perrin DH. *The evaluation process in rehabilitation*. In: Prentice WE, ed. *Rehabilitation Techniques in Sports Medicine*. 2nd ed. St Louis, Mo: Mosby Year Book; 1994:253–276.

Acknowledgments: Provide the names, affiliations, and the nature of their contribution for all persons not included as an author, who played a critical role in the study.

Funding source/trial registration: Details of all funding sources for the work should be provided (including agency name, grant numbers, etc.). Provide the registry name and registration number for all clinical trials (see JPAH Policies below).

Example: “This work was supported by a grant (grant #) from the National Cancer Institute, National Institutes of Health. This study is registered at www.clinicaltrials.gov (No. xxxxx).”

Tables: Each table must be accompanied by an explanatory title so that it is intelligible without specific reference to the text. Column headings and all units of measure must be labelled clearly within each table; abbreviations and acronyms must be fully explained in the table or footnotes without reference to the text.

Figures/Graphics: Graphics should be prepared with clean, crisp lines, and be camera-ready. For shading, stripe patterns or solids (black and white) are better choices than colours. Graphics created on standard computer programs will be accepted. Graphics should be submitted in .tif or .jpg formats only. Each figure and photo must be properly identified. A hard copy may be requested. If photos are used, they should be black and white, clear, and show good contrast.

Human Kinetics Editorial Ethics Policy

APPENDIX 6
Language editor's declaration

Declaration

This is to declare that I, Annette L Combrink

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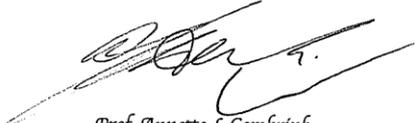
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and telomere length in an urban South African teachers' cohort: the
SABPA study**



Prof. Annette L Combrink
Accredited translator and language editor,
South African Translators' Institute
Membership no. 1000356
Date: 4 November 2014

“Tis grace that brought me safe thus far, and grace will lead me home.”

~ John Newton ~

