



University of Groningen

Dexmedetomidine Induced Deep Sedation Mimics Non-Rapid Eye Movement Stage 3 Sleep

M Ramaswamy, S; Weerink, M A S; Struys, M M R F; B Nagaraj, S

Published in: Sleep

DOI: 10.1093/sleep/zsaa167

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version Publisher's PDF, also known as Version of record

Publication date: 2021

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA): M Ramaswamy, S., Weerink, M. A. S., Struys, M. M. R. F., & B Nagaraj, S. (2021). Dexmedetomidine Induced Deep Sedation Mimics Non-Rapid Eye Movement Stage 3 Sleep: Large Scale Validation using Machine Learning. Sleep, 44(2), [167]. https://doi.org/10.1093/sleep/zsaa167

Copyright Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverneamendment.

Take-down policy

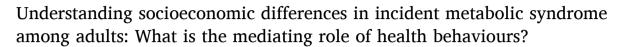
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Contents lists available at ScienceDirect

Preventive Medicine

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



Liza A. Hoveling^{a,*}, Aart C. Liefbroer^{a,b,c}, Ute Bültmann^d, Nynke Smidt^a

^a University of Groningen, University Medical Center Groningen, Department of Epidemiology, PO Box 30.001, 9700 RB Groningen, the Netherlands

^b Netherlands Interdisciplinary Demographic Institute, PO Box 11650, 2502 AR The Hague, the Netherlands

^c Vrije Universiteit Amsterdam, Department of Sociology, De Boelelaan 1081, 1081 HV Amsterdam, the Netherlands

^d University of Groningen, University Medical Center Groningen, Department of Health Sciences, Community and Occupational Medicine, PO Box 30.001, 9700 RB

Groningen, the Netherlands

ARTICLE INFO

Keywords: Metabolic syndrome Socioeconomic factors Physical activity Smoking Alcohol drinking Diet Longitudinal studies Mediation

ABSTRACT

Background: The incidence of metabolic syndrome (MetS) strongly varies by socioeconomic position (SEP), but little is known about the mediating role of health behaviours in this association. This study examines the associations between the SEP measures, education, income and occupational prestige, and incident MetS and whether the associations are mediated by health behaviours, including physical activity, smoking, alcohol intake and diet quality.

Methods: A subsample (n = 85,910) of the adult Lifelines Cohort Study without MetS at baseline was used. MetS was measured at the second assessment (median follow-up time 3.8 years) defined according to the NCEP-ATPIII criteria. Direct associations between SEP, health behaviours and incident MetS were estimated using multivariable logistic regression analyses. The mediating percentages of health behaviours explaining the associations between SEP and incident MetS were estimated using the Karlson-Holm-Breen method. Analyses were independent of age, sex, the other SEP measures and follow-up time.

Results: Education and occupational prestige were inversely associated with MetS. Income was not associated with MetS. Health behaviours explained only partly (13.8%) the association between education and MetS, with smoking as the strongest mediating factor (8.8%). Health behaviours played also a minor role (2.7%) in explaining occupational MetS differences, with physical activity as the strongest suppressing factor (-9.4%). *Conclusion:* Individuals with more years of education or a higher occupational prestige had a lower risk to develop MetS. This was mainly because of non-smoking, less excessive alcohol intake and a higher diet quality. However, individuals with a higher SEP were more often physically inactive.

1. Introduction

Metabolic syndrome (MetS) is a global health problem and can cause high healthcare expenditures. MetS is a cluster of components, including abdominal obesity, elevated blood triglyceride levels, reduced blood high-density lipoprotein (HDL) cholesterol levels, elevated blood pressure, and elevated fasting blood glucose levels, increasing the chances of cardiovascular disease, and all-cause mortality (Alberti et al., 2009). Increasing trends in obesity and overweight are expected to also increase the prevalence of MetS (Grundy, 2016).

Socioeconomic position (SEP) is highly associated with developing MetS, however a clear distinction between different SEP measures, including education, income and occupational prestige is lacking (Blanquet et al., 2019). Education comprises an individual's knowledge, whereas income comprises material resources and occupational prestige comprises social standing (Galobardes et al., 2006a; Galobardes et al., 2006b). Given that different SEP measures reflect different types of resources and therefore may be differently linked to disease mechanisms (Abel, 2008), it is important to examine the associations between all three SEP measures and MetS development.

Understanding the mechanisms linking SEP and developing MetS is important to reduce socioeconomic differences in MetS development. Health behaviours could constitute one class of mediators as there are SEP differences in health behaviours and these health behaviours are major risk factors for developing MetS. Individuals with higher SEP smoke less often, have a healthier diet, but engage in more frequent

* Corresponding author. *E-mail address:* l.a.hoveling@umcg.nl (L.A. Hoveling).

https://doi.org/10.1016/j.ypmed.2021.106537

Received 22 September 2020; Received in revised form 4 February 2021; Accepted 28 March 2021 Available online 31 March 2021

0091-7435/© 2021 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).





alcohol intake compared to their lower SEP counterparts (Broms et al., 2004; Stringhini et al., 2010; Schoufour et al., 2018). Further, inconsistent results are found between SEP and total physical activity (Beenackers et al., 2012). Although physical inactivity, smoking and low diet quality are associated with developing MetS, the link between alcohol intake and MetS is still unclear (Wilsgaard and Jacobsen, 2007; Sun et al., 2012; Julia et al., 2015; Sun et al., 2014). Differences in health behaviours among SEP groups in combination with the strong link between health behaviours and developing MetS, suggest that investigating the mediating role of health behaviours can shed light on a potentially important mechanism behind socioeconomic differences in MetS development.

To our best knowledge, no longitudinal studies have assessed to what extent health behaviours explain socioeconomic differences in MetS development. Therefore, our aim is to investigate which SEP measures are determinants of incident MetS and to what extent SEP differences in incident MetS are explained by health behaviours (Fig. 1).

2. Methods

2.1. Study design and sample

The study sample was derived from the Lifelines Cohort Study (Scholtens et al., 2015). Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of the Netherlands. Lifelines employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. The Lifelines adult study population is broadly representative for the adult population of the North of the Netherlands with respect to socioeconomic characteristics, lifestyle factors, the prevalence of chronic diseases and general health, and risk estimates based on Lifelines data can be generalized to

the population in the North of the Netherlands (Klijs et al., 2015). The study profile of Lifelines, the recruitment and the data collection are described elsewhere (Scholtens et al., 2015).

The current study uses a subsample of 122,906 participants aged 18 years and older, who had complete data for \geq 70% of the variables needed for this study at baseline, and did not have MetS at baseline. Participants who were lost to follow-up at the second assessment (n = 30,936), for whom no MetS status could be determined based on the data of the second assessment (n = 6039) or who had > 30% missing values of the variables needed for this study on the second assessment (n = 21) were excluded from the analyses. Finally, 85,910 (70%) participants were included in the analyses.

2.2. Measures and procedures

2.2.1. Socioeconomic position

SEP was defined by years of education, household equivalent income and occupational prestige measured at baseline. Educational level was recoded into years of education, using the number of years it would take to complete each category by the fastest route possible (Supplementary data table 1 for measurements of the relevant variables in the Lifelines Cohort Study) (De Graaf et al., 2000). Income was recoded as the household equivalent income, by dividing the midpoint of each participant's income category by the square root of his or her household size (OECD, 2018). The amounts were divided by 100, so that the model estimates show the difference in odds ratio (OR) of MetS for a 100-euro difference in household equivalent income. Occupational prestige was recoded from the International Standard Classification of Occupations 2008 (ISCO08) (International Standard Classification of Occupations (ISCO08), n.d.) to the Standard International Occupational Prestige Scale 2008 (SIOPS08) (Treiman, 1977) and divided by 10, so that the model estimates show the difference in OR of MetS for a 10-point difference in occupational prestige score. SIOPS08 is a continuous scale ranging from 0 to 100, indicating low to high occupational prestige (Ganzeboom and Treiman, 1996).

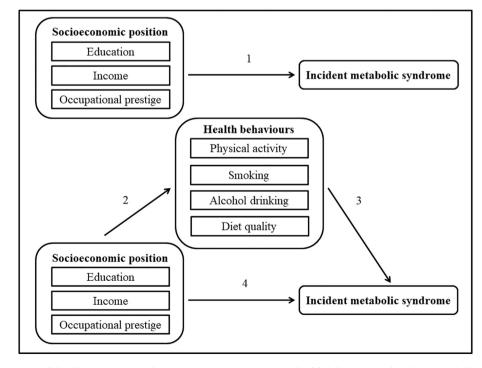


Fig. 1. Graphical representation of the direct associations between socioeconomic position, health behaviours and incident metabolic syndrome and the indirect associations via health behaviours.

2.2.2. Metabolic syndrome

MetS was present if at least three of the five components according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) were present (Alberti et al., 2009). The criteria are: 1) Waist circumference ≥ 102 cm in male or ≥ 88 cm in female; 2) Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or use of blood pressure-lowering medication; 3) Triglycerides ≥ 150 mg/ dL (1.7 mmol/L) or use of medication for elevated triglycerides; 4) HDL cholesterol < 40 mg/dL (1.0 mmol/L) in male or <50 mg/dL (1.3 mmol/ L) in female or use of lipid-lowering medication; 5) Fasting blood glucose level ≥ 100 mg/dL (≥ 5.6 mmol/L) or diagnosis of type 2 diabetes or use of blood glucose-lowering medication. Medication use at baseline was classified according to the Anatomical Therapeutic Chemical coding scheme (World Health Organization, 2011) and at the second assessment classified according to the Lifelines questionnaire. For every participant MetS status (yes/no) was dichotomized.

2.2.3. Health behaviours

Health behaviours were defined by total physical activity, smoking, alcohol intake, and diet quality, measured at baseline. Physical activity was measured using the SQUASH questionnaire and dichtomized based on whether participants were at least 5 days per week moderate to vigorous physically active for at least 30 minutes per day (yes/no) (Health Council of the Netherlands, 2017; Wendel-Vos et al., 2003). Smoking habits were categorized as never, former or current smoker. Alcohol intake measured with the Food Frequency Questionnaire was categorized as no alcohol intake, moderate alcohol intake defined as one glass or less alcohol per day on average, without binge drinking (more than three glasses alcohol on one day for females and more than four glasses alcohol on one day for males) or excessive alcohol intake defined as more than one glass alcohol per day on average or binge drinking (Health Council of the Netherlands, 2015; Molag et al., 2010). Diet quality was based on the Lifelines Diet Score (LLDS) which was based on the 2015 Dutch Dietary Guidelines (Vinke et al., 2018; Kromhout et al., 2016). The LLDS is calculated as the sum of positive and negative food group quintile scores (range 0-48) and relative to the diet quality of the Lifelines population. In the current study, there were no participants with a LLDS of 0 and therefore participants were divided into three groups, according to their LLDS,'poor' diet quality (LLDS 1-16), 'moderate' diet quality (LLDS 17-32) or 'high' diet quality (LLDS 33-48).

2.2.4. Covariates

Age and sex at baseline and time between baseline and the second assessment were used as control variables in all models.

2.3. Statistical analysis

Baseline characteristics concerning demographics, MetS indicators and health behaviours were described. Multivariable logistic regression analysis, controlling for age, sex, other SEP measures at baseline and time between baseline and the second assessment, was used to estimate the direct associations between SEP, health behaviours and incident MetS (Fig. 1, path 1, 2 and 3). The total-, direct- (path 4) and indirect associations between SEP and MetS via health behaviours and the mediating percentages of the health behaviours were estimated using the Karlson-Holm-Breen (KHB) method (Karlson et al., 2012). The KHB method allows comparison of regression coefficients in nested nonlinear models by fixing the residual variance on the same scale in each model. The results of all steps are presented as OR with 99% Confidence Intervals (CI), using physical activity, never smoking, moderate alcohol intake (Sun et al., 2014) and high diet quality as reference categories. Participants were excluded if three or more MetS indicators were missing or if it was not possible to determine whether or not they had MetS when they had provided information on three or four indicators only. Missing values on the SEP measures and the health behaviours were imputed using the Multiple Imputation by Chained Equation

(MICE) method (Azur et al., 2011). MICE was used and 10 datasets were created with 100 iterations for each dataset. The auxiliary variables length and weight were used to give extra information about the incomplete values (White et al., 2011). The imputation model included the independent variables, the covariates, the mediating variables, the dependent variables and auxiliary variables.

In sensitivity analyses, the robustness of the results was evaluated. To assess the potential role of misclassification from medication use at the second assessment, the analyses were repeated for a study sample only including participants who did not use medication during the second assessment (n = 46,218). To assess the potential role of unemployment when assessing the influence of occupational prestige in MetS development, the analyses were repeated for a study sample only including participant who indicated to work at baseline (n = 67,966). Furthermore, a complete case analysis was performed to investigate differences in associations between the study population with imputed data and the complete cases (n = 51,091). In additional analyses, the role of the SEP indicators was further evaluated. SEP conditions are interconnected and the possible mediating role of income and occupational prestige in the causal relation between education and MetS development was assessed. Furthermore, to assess the accumulation of SEP indicators (e.g. a few vears of education, a low income and a low occupational prestige) interactions of the SEP indicators on MetS development were tested. As a final additional analysis, interactions of the SEP indicators with age and sex were tested to investigate whether the associations between SEP and MetS development differed with the associations in the full sample. To allow for multiple testing, interaction terms with p-values < 0.01 were considered to be statistically significant. All analyses were performed using StataMP 13 (64-bit).

3. Results

The mean age of the 85,910 participants was 44.5 (SD 12.4) years and 60.2% was female (Table 1). Most participants had finished secondary vocational education, senior general secondary education or a work-based learning pathway (39.4%), earned a net income between 2500 and 3000 euros per month (17.5%) and had an occupational prestige of 40–50 (e.g. dental assistant) (29.3%). Half of the participants complied with the norm for physical activity (50.5%), most of the participants were never smokers (46.5%), moderate alcohol drinkers (43.8%) and had a diet quality between 17 and 32 (70.8%). Overall, the differences in baseline characteristics between the study sample (n = 85,910) and the excluded participants (n = 36,996) were less than 5% (Supplementary data table 2).

After a median follow-up time of 3.8 years 7.7% of the participants developed MetS. The results of the multivariable logistic regression analyses of the associations between SEP and incident MetS (path 1), SEP and health behaviours (path 2), health behaviours and incident MetS (path 3) and SEP and incident MetS independent of health behaviours (path 4) are presented in Table 2. Individuals with more years of education had a lower likelihood to develop MetS (OR 0.92, 99% CI: 0.91-0.94). To illustrate, a participant who had followed 6 years of education has 11.9% (99% CI: 10.8-13.0%) risk of developing MetS, while if all parameters in the model were kept the same and only the years of education changed to 16 years, the risk of developing MetS decreased to 5.6% (99% CI: 5.2-6.0%) (Fig. 2). Individuals with a higher occupational prestige also had a lower likelihood to develop MetS (OR 0.94, 99% CI: 0.91-0.97). To illustrate, a participant who had an occupational prestige of 20 (e.g. cleaner) has 8.7% (99% CI: 8.1-9.3%) risk of developing MetS, while if all parameters in the model were kept the same and only the occupational prestige changed to 70 (e.g. dentist), the risk of developing MetS decreased to 6.6% (99% CI: 6.0-7.2%) (Fig. 2). When income is used as SEP measure, no association with MetS development was observed (path 1).

Regardless of the SEP measure used, participants with a higher SEP were less often physically active, more often moderate drinkers and had

L.A. Hoveling et al.

Table 1

Baseline characteristics of the study population.

Characteristics	Study population $(n = 85,910)^a$	Missing values (%)	
Demographic			
Age (years), mean (SD)	44.5 (12.4)	0	
Sex (female)	60.2	0	
Socioeconomic			
Education (years), mean (SD)	12.3 (2.4)	2.1	
Low ^b	26.3		
Middle ^b	39.4		
High ^b	32.2		
Occupational prestige (SIOPS08), mean (SD)	43.8 (13.4)	3.9	
Household equivalent income (euros), mean (SD)	1555.5 (572.4)	16.0	
Metabolic syndrome indicators, meeting condition ^c			
Waist circumference ^d	26.2	0	
Triglyceride level ^e	8.8	0	
HDL cholesterol ^f	9.2	0	
Blood pressure ^g	30.5	0	
Glucose level ^h	5.6	0.7	
Health behaviours			
Physical activity ⁱ	50.5	8.7	
Smoking		4.3	
Never smoker	46.5		
Past smoker	30.7		
Current smoker	18.5		
Alcohol intake ^j		1.8	
No alcohol intake	18.9		
Moderate alcohol intake	43.8		
Excessive alcohol intake	35.6		
Dietary quality ^k		12.7	
Poor (LLDS 1–16)	8.5		
Moderate (LLDS 17-32)	70.8		
High (LLDS 33-48)	8.0		

SD: standard deviation; SIOPS08: Standard International Occupational Prestige Scale 2008; HDL: high-density lipoprotein; LLDS: Lifelines Diet Score. ^a % are presented, unless indicated otherwise.

^b Categories according to the Dutch Standard Education Format (Statistics Netherlands, 2018).

^c According to the definition for metabolic syndrome by NCEP-ATPIII.

 $^{d} \geq$ 102 cm in male or \geq 88 cm in female.

 $^{e} \geq$ 1.70 mmol/L or use of medication for elevated triglycerides.

 $^{\rm f}$ < 1.0 mmol/L in male or < 1.3 mmol/L in female or use of lipid-lowering medication.

^g Systolic blood pressure \geq 130 mmHg or diastolic blood pressure \geq 85 mmHg or use of blood pressure-lowering medication.

^h Fasting blood glucose level \geq 5.6 mmol/L or diagnosis of type 2 diabetes or use of blood glucose-lowering medication.

ⁱ Complies with the norm of at least 30 min of moderately intensive exercise at least five days a week.

^j According to the guidelines of the Health Council of the Netherlands.

^k According to the Lifelines Diet Score.

more often a high diet quality compared to participants with a lower SEP. Participants with more years of education or a higher occupational prestige were less often former or current smokers (path 2). Finally, participants with unhealthy behaviours had a higher risk to develop MetS (path 3).

The results of the multivariable total-, direct- and indirect associations and mediating percentages using the KHB method are presented in Table 3. The lower risk of MetS for higher educated was for 13.8% mediated by health behaviours. The lower risk of MetS for participants with a higher occupational prestige was for 2.7% mediated by health behaviours. The lower risk for higher educated and participants with a higher occupational prestige was mainly due to less smoking, a higher diet quality and less excessive alcohol intake. However, participants with a higher education and a higher occupational prestige were more physically inactive. The (in)direct association between income and incident MetS was not significant and therefore health behaviours do not mediate this association.

Sensitivity analyses did not show substantively different results compared to the results of the full sample when using a sample including only participants who did not use medication during the second assessment, a study sample including only employed participants or a study sample including only complete cases (Table 4 for the associations between SEP and MetS development and supplementary data tables 3–8 for detailed analyses). The first additional analysis showed that occupational prestige (3.5%) and a combination of occupational prestige and income (21.8%) mediated the causal path between education and MetS development, while income alone did not mediate this path (Supplementary data table 9). Overall, the second additional analysis did not show evidence for an accumulation of SEP indicators in MetS development and health behaviours (p-values > 0.01 for interactions). However, an accumulation of SEP indicators was observed for being physically inactive (Supplementary data table 10). The third additional analysis showed no differences for the associations between income and MetS development and occupational prestige and MetS development between the different strata (i.e. female and male or age groups < 45years and \geq 45 years) (p-values between 0.048 and 0.546 for interactions) (Supplementary data tables 11-18). Differences between the strata were observed for educational differences in MetS development and were partly explained by health behaviours, varying from 12.0% for younger adults, 5.7% for older adults, 12.1% for males and 16.0% for females with smoking in all groups as the strongest mediating factor. The interaction between sex and occupational prestige in MetS development was borderline significant (p-value = 0.011 for interaction), with no occupational prestige differences in MetS development for males and the occupational prestige differences were partly explained by health behaviours (6.7%) for females. Although small differences between the strata were observed for the associations between SEP and MetS development and for the associations between the SEP indicators

L.A. Hoveling et al.

Table 2

Multivariable logistic regression analysis of the direct associations between socioeconomic position, health behaviours and incident metabolic syndrome.

	Education	Occupational prestige	Income OR (99% CI)	
	OR (99% CI)	OR (99% CI)		
Path 1. SEP and MetS	0.92 (0.91–0.94)	0.94 (0.91–0.97)	0.99 (0.99–1.00)	
Path 2. SEP and health behaviours				
Physical activity				
No	1.04 (1.03–1.05)	1.11 (1.09–1.13)	1.01 (1.00-1.01)*	
Smoking				
Former	0.94 (0.93-0.95)	0.99 (0.97-1.01)	1.02 (1.01-1.02)	
Current	0.86 (0.85-0.88)	0.94 (0.92-0.96)	1.01 (1.00-1.01)*	
Alcohol intake				
No	0.93 (0.91-0.94)	0.94 (0.92–0.96)	0.97 (0.97-0.98)	
Excessive	0.96 (0.95-0.97)	0.99 (0.97-1.01)	1.01 (1.01–1.02)	
Diet quality				
Moderate (LLDS 17–32)	0.89 (0.87-0.91)	0.98 (0.94–1.00)*	0.99 (0.98–0.99)	
Poor (LLDS 1–16)	0.78 (0.76-0.80)	0.90 (0.86-0.94)	0.98 (0.97-0.99)	
Path 3. Health behaviours and MetS				
Physical activity				
No	1.27 (1.18–1.37)	1.27 (1.18–1.37)	1.27 (1.18–1.37)	
Smoking				
Former	1.13 (1.04–1.22)	1.13 (1.04–1.22)	1.13 (1.04–1.22)	
Current	1.45 (1.32–1.59)	1.45 (1.32–1.59)	1.45 (1.32–1.59)	
Alcohol intake				
No	1.40 (1.28–1.54)	1.40 (1.28–1.54)	1.40 (1.28–1.54)	
Excessive	1.07 (0.98–1.15)	1.07 (0.98–1.15)	1.07 (0.98–1.15)	
Diet quality				
Moderate (LLDS 17–32)	1.17 (1.02–1.35)	1.17 (1.02–1.35)	1.17 (1.02–1.35)	
Poor (LLDS 1–16)	1.34 (1.12–1.62)	1.34 (1.12–1.62)	1.34 (1.12–1.62)	
Path 4. SEP and MetS independent of health behaviours				
Physical activity	0.92 (0.90-0.94)	0.94 (0.91–0.97)	0.99 (0.99–1.00)	
Smoking	0.93 (0.91-0.94)	0.94 (0.92–0.97)	0.99 (0.99–1.00)	
Alcohol intake	0.92 (0.91-0.94)	0.94 (0.92–0.97)	1.00 (0.99–1.00)	
Diet quality	0.92 (0.91-0.94)	0.94 (0.92–0.97)	1.00 (0.99–1.00)	
Health behaviours combined	0.93 (0.91-0.95)	0.94 (0.91-0.97)	1.00 (0.99–1.00)	

OR: odds ratio; CI: confidence interval; SEP: socioeconomic position; MetS: metabolic syndrome; the analyses were independent of years of education, household equivalent income, occupational prestige, age and sex at baseline and time between baseline and the second assessment; reference categories for the health behaviours were physically active, never smoker, moderate alcohol intake and high diet quality.

 * P < 0.01 for associations with 1.00 at the lower or upper bound of the CI.

and MetS development combined for age and sex (e.g. education*age*sex) the results are in line with the results in the full sample (Supplementary data tables 19–26).

4. Discussion

The aim of this study was to investigate which SEP measures are determinants of MetS development and to what extent SEP differences in incident MetS are explained by health behaviours. Education and occupational prestige were found to be strong determinants of MetS development, whereas income was not associated with MetS development. An individual who has an occupational prestige on the SIOPS08 scale (International Standard Classification of Occupations (ISCO08), n. d.) of 20 has a 1.3-fold higher risk of developing MetS than an individual who has an occupational prestige of 70. The role of education is even more important. An individual who has completed 6 years of education has a more than two-fold higher risk of developing MetS than an individual who has completed 16 years of education. These associations underline the conclusions of a recent meta-analysis investigating the associations between SEP and MetS (Blanquet et al., 2019). Although, based on our additional analyses, we are aware that SEP indicators are interrelated, and our results show that income and occupational prestige partly mediate the effect of education in MetS development, our results also show independent relationships for the SEP indicators on the outcomes. Our study shows the importance of distinguishing between three possible SEP measures and of conceptualizing SEP as a multidimensional concept, because not only years of education, but also occupational prestige has an independent relationship with MetS development. Education and occupational prestige both reflect intellectual and cognitive resources, which seem to be more important in explaining MetS development in the Netherlands than the material resources of an individual captured by income. The Netherlands has a well-developed welfare state, where income does not strongly influence access to healthcare, but in countries with a less well-developed welfare state, financial resources could be more important for accessing healthcare facilities.

Overall, our results show positive associations between SEP and healthy behaviours. Higher educated participants smoke less, have a higher diet quality and are less often excessive alcohol drinkers, consistent with previous research (Broms et al., 2004; Stringhini et al., 2010; Schoufour et al., 2018). This was also observed for participants with a higher occupational prestige. At the same time, higher educated participants and participants with a higher occupational prestige are less physically active. Consistent with previous work, our results clearly show that physical inactivity, excessive alcohol intake, current or former smoking and poor diet quality increase the risk of MetS (Wilsgaard and Jacobsen, 2007; Sun et al., 2012; Julia et al., 2015). The higher MetS risk of participants who did not drink alcohol compared to moderate alcohol drinkers could be because the category of non-drinkers includes both lifetime abstainers and former drinkers. Although we do not have data to substantiate this, these groups could be different in terms of their risk of developing MetS as former alcohol drinkers could be individuals who stopped their drinking in response to poor health (Sun et al., 2014).

Educational differences in MetS development were better explained by health behaviours than were occupational prestige differences in MetS development. Education is strongly associated to the development of healthy behaviours in early life, which shape health behaviours and health outcomes such as MetS in later life. Education is, in contrast to other SEP measures, more often seen as a stable marker for SEP and is less susceptible to reverse causation (Geyer et al., 2006).

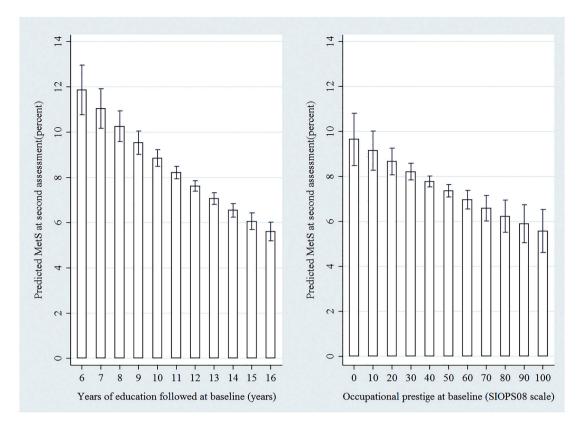


Fig. 2. Bar charts of the risk of metabolic syndrome at second assessment in percentage (with 99% CI) per year of education followed at baseline (left) and occupational prestige at baseline (right).

Table 3

Multivariable mediation analysis of health behaviours in the associations between socioeconomic position and incident metabolic syndrome using the Karlson-Holm-Breen method.

	Education OR (99% CI)		Occupational prestige OR (99% CI)		Income
					OR (99% CI)
Total association	0.92		0.94 (0.91–0.97)	1.00
	(0.90–0	(0.90-0.94)		(0.99 - 1.00)	
Direct association	0.93 0.		0.94 (0.91–0.97)	1.00
	(0.91–0	.91–0.95)		(0.99 - 1.00)	
Indirect	0.99		1.00 (1.00-1.00)*		1.00
association	(0.99–0	.99)			(1.00–1.00)
		Percentag	je	Percentage	Percentage
		(%)		(%)	(%)
Mediating effects					
Physical activity		-2.5		-9.4	-10.8
Smoking		8.8		4.9	-10.8
Alcohol intake		3.7		5.1	32.9
Diet quality		3.8		2.1	7.2
Health behaviours combined		13.8		2.7	18.6

OR: odds ratio; CI: confidence interval; SEP: socioeconomic position; MetS: metabolic syndrome; the analyses were independent of years of education, household equivalent income, occupational prestige, age and sex at baseline and time between baseline and the second assessment.

P < 0.01 for associations with 1.00 at the lower or upper bound of the CI.

Smoking was the most important health behaviour to explain educational differences in MetS development. While a combination of the health behaviours explained occupational prestige differences in MetS development. Participants with a higher occupational prestige were less likely to be physically active, but the lower risk of MetS development for participants with a higher occupational prestige holds. These results of partial mediation by health behaviours support other study findings assessing the potential modifiable risk factors for SEP differences in type 2 diabetes (Robbins et al., 2005; Williams et al., 2010; Smith et al., 2013; Kumari et al., 2004; Stringhini et al., 2012; Maty et al., 2011). In our study, we examined the mediating role of total physical activity in the SEP – MetS relationship. Among individuals active on the labour market, it would be interesting to further examine whether this mediating role operates in the same way for leisure-time physical activity and occupational physical activity. Individuals with a higher SEP could on average perform more leisure-time physical activity and less occupational physical activity, while for individuals with a lower SEP this could be the other way around (Coenen et al., 2018).

This study has several important strengths. First, the longitudinal design and the large study sample allowed us to study the relationship between SEP and the development of MetS. Second, our results extend previous work by assessing not only type 2 diabetes as health outcome, but focusing on MetS to assess socioeconomic health differences. Third, results are likely to be generalizable to the population of the North of the Netherlands (Klijs et al., 2015). This study also has some limitations. First, the self-reported health behaviours were measured at baseline. As the associations between SEP, the health behaviours and MetS were consistent with the literature, we assume that health behaviours have not changed much over time. Second, the presence of MetS at the second assessment was determined without taking specific medication use at the second assessment into account. However, a sensitivity analysis including only participants who did not use prescribed medication, did not change the results and therefore we assume that the associations would not change if specific medication use at the second assessment was taken into account.

Table 4

Multivariable logistic regression analysis of the direct associations between socioeconomic position and incident metabolic syndrome for the full sample, sensitivity analyses and additional analyses.

	Education	Occupational prestige	Income OR (99% CI)	
	OR (99% CI)	OR (99% CI)		
Full sample (n = 85,910)	0.92 (0.91–0.94)	0.94 (0.91–0.97)	0.99 (0.99–1.00)	
Sensitivity analyses				
Participants who did not use medication at the second assessment $(n = 46,218)$	0.91 (0.89-0.94)	0.97 (0.92-1.02)	1.00 (0.99-1.01)	
Participants who were employed at baseline $(n = 67,966)$	0.92 (0.90-0.93)	0.95 (0.91-0.98)	1.00 (0.99-1.00)	
Complete cases $(n = 51,091)$	0.92 (0.90-0.94)	0.93 (0.90–0.97)	1.00 (0.99–1.01)	
Additional analyses				
Male participants ($n = 34,206$)	0.92 (0.90-0.95)	0.97 (0.92-1.02)	1.00 (0.99-1.01)	
Female participants ($n = 51,704$)	0.92 (0.90-0.94)	0.93 (0.89-0.97)	0.99 (0.98-1.00)	
Participants under the age of 45 $(n = 42,640)$	0.87 (0.85-0.89)	0.95 (0.90-1.00)*	1.00 (0.99-1.01)	
Participants aged 45 or older ($n = 43,270$)	0.92 (0.90-0.94)	0.96 (0.92-1.00)	1.00 (0.99-1.01)	
Male participants under the age of 45 $(n = 16,638)$	0.87 (0.84-0.90)	1.02 (0.95–1.09)	1.01 (0.99-1.02)	
Male participants aged 45 or older ($n = 17,568$)	0.95 (0.92-0.98)	0.95 (0.89-1.01)	1.00 (0.98-1.01)	
Female participants under the age of 45 ($n = 26,002$)	0.87 (0.83-0.91)	0.89 (0.83-0.96)	0.99 (0.98-1.01)	
Female participants aged 45 or older ($n = 25,702$)	0.90 (0.88-0.93)	0.97 (0.92-1.02)	1.00 (0.99-1.02)	

OR: odds ratio; CI: confidence interval; SEP: socioeconomic position; MetS: metabolic syndrome; the analyses were independent of years of education, household equivalent income, occupational prestige, age and sex at baseline and time between baseline and the second assessment.

 * P < 0.01 for associations with 1.00 at the lower or upper bound of the CI.

5. Conclusion

Findings in this study suggest that interventions to decrease MetS development and improve health behaviours may reduce, but not eliminate, SEP differences in developing MetS. The fact that health behaviours did not account entirely for the associations between SEP and MetS development shows that efforts in future research should focus on other mediating pathways. Future research should not only focus on health behaviours but also on social- and environmental levels of socioeconomic disadvantaged groups, such as life events and selfmanagement. Furthermore, instead of studying health behaviours in general, differentiation within the four health behaviours, e.g. differentiating for domains of physical activity, alcoholic drinks and food groups, would be an interesting avenue of future research. In conclusion, each SEP measure is differently associated with the development of MetS. If we want to reduce socioeconomic differences in MetS development, and ensure that all groups benefit from it, individuals with a lower SEP need to stop smoking and attention should be paid to alcohol intake and diet quality and individuals with a higher SEP need to be more aware of their physical activity.

Funding

This work was supported by The Netherlands Organization for Health Research and Development (ZonMw) [grant number 531003011]. ZonMw has not been involved in the research process.

Ethical approval and consent to participate

Ethical approval for the Lifelines Cohort Study was provided by the medical ethical committee of the University Medical Center Groningen, the Netherlands (Ethics Approval ID: 2007/152).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The data generated and supporting the findings of the current study have been obtained from the Lifelines Cohort Study.

Code availability

The generated dataset is not publicly available as it is created and used under license from the Lifelines Cohort Study. Data from the Lifelines Cohort Study is available on request (www.lifelines.nl).

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Acknowledgments

We wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centres delivering data to Lifelines and all the study participants. The Lifelines Biobank initiative has been made possible by subsidy from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the University Medical Center Groningen (UMCG the Netherlands), University Groningen and the Northern Provinces of the Netherlands.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ypmed.2021.106537.

References

- Abel, T., 2008. Cultural capital and social inequality in health. J. Epidemiol. Community Health 62 (7), e13. https://doi.org/10.1136/jech.2007.066159.
- Alberti, K.G.M.M., et al., Oct. 2009. Harmonizing the metabolic syndrome. Circulation 120 (16), 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.
- Azur, M.J., Stuart, E.A., Frangakis, C., Leaf, P.J., Mar. 2011. Multiple imputation by chained equations: what is it and how does it work? Int. J. Methods Psychiatr. Res. 20 (1), 40–49. https://doi.org/10.1002/mpr.329.
- Beenackers, M.A., et al., 2012. Socioeconomic inequalities in occupational, leisure-time, and transport related physical activity among European adults: a systematic review. Int. J. Behav. Nutr. Phys. Act. https://doi.org/10.1186/1479-5868-9-116.
- Blanquet, M., Legrand, A., Pélissier, A., Mourgues, C., 2019. Socio-economics status and metabolic syndrome: a meta-analysis. Diabetes Metab. Syndr. Clin. Res. Rev. https:// doi.org/10.1016/j.dsx.2019.04.003.
- Broms, U., Silventoinen, K., Lahelma, E., Koskenvuo, M., Kaprio, J., 2004. Smoking cessation by socioeconomic status and marital status: The contribution of smoking behavior and family background. Nicotine Tob. Res. https://doi.org/10.1080/ 14622200410001696637.

L.A. Hoveling et al.

Coenen, P., et al., 2018. Can socioeconomic health differences be explained by physical activity at work and during leisure time? Rationale and protocol of the active worker individual participant meta-analysis. BMJ Open 8 (10), 1–10. https://doi.org/ 10.1136/bmjopen-2018-023379.

De Graaf, N.D., De Graaf, P.M., Kraaykamp, G., 2000. Parental cultural capital and educational attainment in the Netherlands: a refinement of the cultural capital perspective. Sociol. Educ. 73 (2), 92–111.

- Galobardes, B., Shaw, M., Lawlor, D.A., Lynch, J.W., Smith, G.D., 2006a. Indicators of socioeconomic position (part 1). J. Epidemiol. Community Health. https://doi.org/ 10.1136/jech.2004.023531.
- Galobardes, B., Shaw, M., Lawlor, D.A., Lynch, J.W., Smith, G.D., 2006b. Indicators of socioeconomic position (part 2). J. Epidemiol. Community Health. https://doi.org/ 10.1136/jech.2004.028092.

Ganzeboom, H.B.G., Treiman, D.J., 1996. Internationally comparable measures of occupational status for the 1988 International Standard Classification of Occupations. Soc. Sci. Res. 25 (3), 201–239. https://doi.org/10.1006/ ssre.1996.0010.

Geyer, S., Hemström, Ö., Peter, R., Vågerö, D., 2006. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. J. Epidemiol. Community Health 60 (9), 804–810. https://doi.org/10.1136/jech.2005.041319.

Grundy, S.M., 2016. Metabolic syndrome update. Trends Cardiovasc. Med. 26 (4), 364–373. https://doi.org/10.1080/13607863.2015.1023766.

Health Council of the Netherlands, 2015. Achtergronddocument Alcohol. Health Council of the Netherlands.

Health Council of the Netherlands, 2017. Physical Activity Guidelines 2017, pp. 1–45 https://doi.org/publication no. 2017/08e.

International Standard Classification of Occupations (ISCO08) [Online]. Available: https://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm.

Julia, C., et al., 2015. The nutrient profile of foods consumed using the british food standards agency nutrient profiling system is associated with metabolic syndrome in the SU.VI.MAX cohort. J. Nutr. https://doi.org/10.3945/jn.115.213629.

Karlson, K.B., Holm, A., Breen, R., 2012. Comparing regression coefficients between same-sample nested models using logit and probit: a new method. Sociol. Methodol. 42 (1), 286–313.

Klijs, B., Scholtens, S., Mandemakers, J.J., Snieder, H., Stolk, R.P., Smidt, N., 2015. Representativeness of the LifeLines cohort study. PLoS One 10 (9), 1–12. https://doi. org/10.1371/journal.pone.0137203.

Kromhout, D., Spaaij, C.J.K., De Goede, J., Weggemans, R.M., Dutch, C., Guidelines, D., 2016. The 2015 Dutch Food-based Dietary Guidelines, 70, pp. 869–878. https://doi. org/10.1038/ejcn.2016.52 no. 8.

Kumari, M., Head, J., Marmot, M., 2004. Prospective study of social and other risk factors for incidence of type 2 diabetes in the Whitehall II study. Arch. Intern. Med. https://doi.org/10.1001/archinte.164.17.1873.

- Maty, S.C., Everson-rose, S.A., Haan, M.N., Raghunathan, T.E., Kaplan, G.A., 2011. Education, Income, Occupation, and the 34-year Incidence (1965–99) of Type 2 Diabetes in the Alameda County Study, 34, pp. 1274–1281. https://doi.org/ 10.1093/ije/dyi167.Education no. 6.
- Molag, M.L., et al., 2010. Selecting informative food items for compiling food-frequency questionnaires: comparison of procedures. Br. J. Nutr. 104 (3), 446–456. https://doi. org/10.1093/ije/dyi167.Education.

OECD, 2018. Compare Your Income - Methodology and Conceptual Issues, 2018.

Robbins, J.M., Vaccarino, V., Zhang, H., Kasl, S.V., 2005. Socioeconomic status and diagnosed diabetes incidence. Diabetes Res. Clin. Pract. 68 (3), 230–236. https:// doi.org/10.1016/j.diabres.2004.09.007.

Scholtens, S., et al., 2015. Cohort Profile: LifeLines, a three-generation cohort study and biobank. Int. J. Epidemiol. 44 (4), 1172–1180. https://doi.org/10.1093/ije/dyu229.

Schoufour, J.D., et al., 2018. Socio-economic indicators and diet quality in an older population. Maturitas 107 (October 2017), 71–77. https://doi.org/10.1016/j. maturitas.2017.10.010.

Smith, P.M., Smith, B.T., Mustard, C.A., Lu, H., Glazier, R.H., 2013. Estimating the direct and indirect pathways between education and diabetes incidence among Canadian men and women: a mediation analysis. Ann. Epidemiol. 23 (3), 143–149. https:// doi.org/10.1016/j.annepidem.2012.12.012.

Statistics Netherlands, 2018. Standaard Onderwijsindeling. Statistics Netherlands.

Stringhini, S., et al., 2010. Association of socioeconomic position with health behaviors and mortality. The Whitehall II study. NIH Public Access 303 (12), 1159–1166. https://doi.org/10.1001/jama.2010.297.Association.

- Stringhini, S., et al., 2012. Contribution of modifiable risk factors to social inequalities in type 2 diabetes: prospective Whitehall II cohort study. BMJ 345 (7875), 1–11. https://doi.org/10.1136/bmj.e5452.
- Sun, K., Liu, J., Ning, G., 2012. Active Smoking and Risk of Metabolic Syndrome : A Meta-Analysis of Prospective Studies, 7. https://doi.org/10.1371/journal. pone.0047791 no. 10.
- Sun, K., Ren, M., Liu, D., Wang, C., Yang, C., Yan, L., 2014. Alcohol consumption and risk of metabolic syndrome: A meta-analysis of prospective studies. Clin. Nutr. https:// doi.org/10.1016/j.clnu.2013.10.003.

Treiman, D.J., 1977. Occupational Prestige in Comparative Perspective. Press, New York Acad.

- Vinke, P.C., Corpeleijn, E., Dekker, L.H., Jacobs, D.R., Navis, G., Kromhout, D., 2018. Development of the food-based Lifelines Diet Score (LLDS) and its application in 129,369 Lifelines participants. Eur. J. Clin. Nutr. 72 (8), 1111–1119. https://doi. org/10.1038/s41430-018-0205-z.
- Wendel-Vos, G.C.W., Schuit, A.J., Saris, W.H.M., Kromhout, D., 2003. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. J. Clin. Epidemiol. 56 (12), 1163–1169. https://doi.org/10.1016/S0895-4356(03)00220-8.

White, I.R., Royston, P., Wood, A.M., 2011. Multiple imputation using chained equations: issues and guidance for practice. Stat. Med. 30 (4), 377–399. https://doi. org/10.1002/sim.4067.

Williams, E.D., Tapp, R.J., Magliano, D.J., Shaw, J.E., Zimmet, P.Z., Oldenburg, B.F., 2010. Health behaviours, socioeconomic status and diabetes incidence: the Australian Diabetes Obesity and Lifestyle Study (AusDiab). Diabetologia 53 (12), 2538–2545. https://doi.org/10.1007/s00125-010-1888-4.

- Wilsgaard, T., Jacobsen, B.K., 2007. Lifestyle factors and incident metabolic syndrome. The Tromsø Study 1979–2001. Diabetes Res. Clin. Pract. 78 (2), 217–224. https:// doi.org/10.1016/j.diabres.2007.03.006.
- World Health Organization, 2011. The Selection and Use of Essential Medicines, 2019 no. 965.