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ASSOCIATION BETWEEN SIESTA (DAYTIME SLEEP), DIETARY PATTERNS AND THE PRESENCE OF METABOLIC SYNDROME IN ELDERLY LIVING IN MEDITERRANEAN AREA (MEDIS STUDY): THE MODERATING EFFECT OF GENDER

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ABSTRACT

Objectives: Several lifestyle parameters including diet, physical activity and sleep were associated in isolation with the presence of Metabolic Syndrome (MetS) in adults, to date there is a paucity of studies which evaluated their combined role aging populations and especially with respect to gender. Therefore, the aim of the present study was to provide a global consideration of the lifestyle factors associated with MetS among elderly individuals. **Design:** Cross-sectional observational study. **Setting:** 21 Mediterranean islands and the rural Mani region (Peloponnesus) of Greece. **Participants:** during 2005-2015, 2749 older (aged 65-100 years) from were voluntarily enrolled in the study. **Measurements:** Dietary habits, energy intake, physical activity status, socio-demographic characteristics, lifestyle parameters (sleeping and smoking habits) and clinical profile aspects were derived through standard procedures. The presence of MetS was defined using the definition provided by NCEP ATP III (revised) and cluster analysis was used to identify overall dietary habit patterns. **Results**: The overall prevalence of MetS in the study sample was 36.2%, but occurred more frequently in females (40.0% vs. 31.8%, respectively, p=0.03). Individuals with MetS were more likely to sleep during the day (89.4% vs. 76.8% respectively, p=0.039) and frequent '*siesta*' was positively linked to the odds of MetS presence in females (Odds Ratio (OR) =3.43, 95% Confidence Intervals (CI): 1.08-10.9), but not for men (p=0.999). The lower carbohydrate (i.e., 45.2% of total daily energy, 120±16gr/day) dietary cluster was inversely associated with the odds for MetS presence, but only for men (OR=0.094, 95%CI: 0.010-0.883). **Conclusions:** Lifestyle parameters including sleep and diet quality are strongly associated with the presence of MetS in elderly cohort, but different their level of influence appears to be different, depending on gender. Further research is needed to better consider the role of lifestyle characteristics in the management of MetS in clinical practice.

Key words: Metabolic Syndrome; Sleep; Elderly; Diet; Lifestyle; MEDIS; siesta; Mediterranean-type diet

Introduction

Metabolic syndrome (MetS) is a complex disorder, defined as a cluster of interacting metabolic abnormalities which includes; insulin resistance, central obesity, dyslipidemia, impaired endothelial function, increased arterial blood pressure levels, hypercoagulation and low-grade inflammation (1, 2). MetS diagnosis is associated with an increased risk of developing type 2 diabetes mellitus, atherogenesis and cardiovascular disease (CVD), thus, its management is in the pivotal point for CVD primary prevention (3). However, MetS is an increasingly prevalent condition, present in approximately 20-30% of the adult population worldwide (4), with prevalence increasing with age, reaching almost 60% in older cohorts (5). Additionally, this apparent exponential increase in incidence appears to parallel that seen in obesity which has become a modern epidemic challenging public health systems. This has led to numerous studies investigating the pathophysiology underpinning MetS in order to decrease in its rate of incidence (6-9)

A number of lifestyle parameters have been linked to the risk of developing MetS including sedentary lifestyle (10), unhealthy dietary habits (11) and more recently, suboptimal quantities of sleep (12, 13) have been associated with higher risk of developing MetS within other health outcomes. More specifically, with respect to physical activity levels, subjects who engage in vigorous physical activity decreased their odds of developing MetS by up to 40% (10), whilst adherence to a Mediterranean-type diet offers further protection against the development of MetS (14). Moreover, recent research suggests that adherence to Mediterranean diet is linked to better physical performance among elderly (15), suggesting the potential of a synergistic effect against MetS. With respect to sleeping habits and behavior, not only the quantity of sleeping hours appears to be predictive (12), but also the engaging in daytime sleep habits, typically known as "*siesta*" that lasts more than one hour has been proposed as an aggravating factor that is associated with increased odds of

MetS presence in middle-aged individuals. The latter finding was shown to be a significant relationship only for females, suggesting a differentiation between the two genders in the risk factors for the development of MetS (16). This has led to increased interest and more focused investigations of how MetS appears to manifest differently in males and females, highlighting the emerging need to consider different therapeutic and therefore preventative approaches for the two genders (17).

To date, despite the research that has evaluated the effects of the aforementioned lifestyle parameters on the presence and development of MetS, no attempt has been made to incorporate these parameters into the same analysis in order to explore potential interactions or synergistic effects between these factors. Therefore, the aim of the present study was to investigate potential interactions between lifestyle factors that may link the presence of MetS with dietary patterns, sleeping habits, physical activity status and other health characteristics of an elderly cohort.

Materials and methods

Methodology

The Mediterranean Islands (MEDIS) study is an ongoing, large-scale, multinational project in the Mediterranean region, which is exploring the association between lifestyle habits, psycho-social characteristics and living environment, on cardiometabolic factors, among older people (>65 years), residing in the Mediterranean area.

The Study's sample

Between 2005-2015, a random population-based, multistage sampling method (i.e., age group, 3 levels (65 - 75, 75 - 85, 85 ±) and 2 sex levels) was used to voluntarily enrol older men and women people from 22 Mediterranean islands: including Malta Republic (n=250), Sardinia (n=60) and Sicily (n=50) in Italy, Mallorca and Menorca (n=111), Republic of Cyprus (n=300), Gökçeada (n=55) in Turkey, and the Greek islands of Lesvos (n=142), Samothraki (n=100), Cephalonia (n=115), Crete (n=131), Corfu (n=149), Limnos (n=150), Ikaria (n=76), Syros (n=151), Naxos (n=145), Zakynthos (n=103), Salamina (n=147), Kassos (n=52), Rhodes and Karpathos (n=149), Tinos (n=129), as well as the rural region of east Mani (n=295, 157 men aged 75±7 years and 138 women aged 74±7 years) (a Greek peninsula, which is in the southeast, continental area of Europe, with a total population of 13,005 people (census 2011), which has morphological and cultural specificities, which are not common across in the rest of Greece. The participation rate varied according to region, from 75% to 89%. Thus, for the present work information from 1,369 men, aged 75±8 years and 1,380 women, aged 74±7 years were analysed.

Individuals who resided in assisted-living centres, had a clinical history of cardiovascular disease (CVD) or cancer, or had left the island for a considerable period of time during their life (i.e., >5 years) were excluded from participating in the study; these criteria were applied because the study aimed to assess lifestyle patterns that were not a response of individuals modifying how they live due to existing chronic health care conditions or by environmental factors, other than their living milieu. A multidisciplinary group of health scientists (physicians, dietitians, public health nutritionists and nurses) with experience in field investigation collected all the required information using a quantitative questionnaire and standard procedures.

Bioethics

The study followed the ethical considerations provided by the World Medical Association (52^{nd} WMA General Assembly, Edinburgh, Scotland; October 2000). The Institutional Ethics Board of Harokopio University approved the study design (16/19-12-2006). Participants were informed about the aims and procedures of the study and gave their consent prior to being interviewed.

Evaluation of clinical characteristics

All of the measurements taken in the different study centres were standardized and the questionnaires were translated into all of the cohorts' languages following the World Health Organization (WHO) translation guidelines for tools assessment (www.who.int/substance_abuse/research_tools/translation/en/).

Height and weight were measured using standard procedures to attain body mass index (BMI) scores (kg/m^2). Waist circumference (cm) was measured at the midpoint between the 12^{th} rib and the iliac crest and hip circumference (cm) was measured around the widest part of the buttocks. Central adiposity was defined as waist circumference greater than 102 cm for men and 88 cm for women. Diabetes mellitus (type 2) was determined by fasting plasma glucose tests and was analysed in accordance with the American Diabetes Association diagnostic criteria (glycated haemoglobin A1C>6.5% or fasting blood glucose levels greater than 126 mg/dl or 2-h plasma glucose > 200 mg/dl during an oral glucose tolerance test-OGTT- or a random plasma glucose > 200 mg/dl or they have been already diagnosed with diabetes). Participants who had blood pressure levels above 140/90 mmHg or used antihypertensive medications were classified as hypertensive. Fasting blood lipids levels (HDL-, LDL-cholesterol and triglycerides) were also recorded and hypercholesterolemia was defined as total serum cholesterol levels greater than 200 mg/dL or the use of lipid-lowering agents according to the NCEP ATP III guidelines (18). The coefficient of variation for the blood measurements was less than 5%. The presence of MetS was defined using the definition provided by NCEP ATP III (revised); three or more of the following metabolic components present: waist circumference ≥102 cm for males or ≥88 cm for females;

triglycerides level ≥150 mg/dl; HDL cholesterol level <40 mg/dL for males or <50 mg/dL for females; blood pressure ≥130/85 mmHg; fasting blood glucose ≥100 mg/dL(19).

Evaluation of lifestyle and socio-demographic characteristics

Dietary habits were assessed through a semi-quantitative, validated and reproducible food-frequency questionnaire (20). Trained dietitians estimated the mean daily energy intake and the mean percentage of total energy derived from dietary carbohydrates. To evaluate the level of adherence to the Mediterranean diet, the MedDietScore (possible range 0-55) was used (21). Higher values for this diet score being indicative of greater adherence to the Mediterranean diet. Participants were also encouraged to report the duration of following their dietary pattern (i.e., number of years this pattern had been in place). Basic socio-demographic characteristics such as age, sex, occupational status, household composition, education level (described as number of school years), residing in rural or urban area, as well as lifestyle characteristics, such as smoking habits and physical activity status, data on frequency of sleeping during the day (siesta) defined as having a siesta for more than five days per week (22), were also recorded. Current smokers were defined as smokers at the time of the interview, whereas former smokers were defined as those who previously smoked, but had not done so for a year or more. Current and former smokers were defined as had '*ever smokers*'. The remaining participants were defined as occasional or non-smokers. Physical activity was evaluated in MET-minutes per week, using the shortened, translated and validated into Greek, version of the self-reported International Physical Activity Questionnaire (IPAQ) (23). Frequency (times per week), duration (minutes per session) and intensity of physical activity during sports, occupation and/or leisure activities were assessed. Participants were instructed to report only episodes of activity lasting at least 10 min, since this is the minimum required to achieve health benefits. Physically active individuals were defined those who reported at least 3 MET-min. Daily walking time was calculated by using the IPAQ question about walking (times per week and average time spent).

Further in depth details about the MEDIS study protocols have been extensively been published elsewhere (24, 25).

Statistical analysis

Continuous variables are expressed as mean±standard deviation for variables following assessing for normal distribution, or median (inter-quartile range) for variables not following normal distribution. Normality was tested using P-P plots. Differences in continuous variables between MetS and non-MetS subjects were evaluated with the Student's t-test for normally distributed parameters and the Mann-Whitney test for non-parametric variables. Nominal variables are presented as frequencies and relative frequencies (%). Pearson's Chi-square test was used to assess the association between two nominal variables. In order to group subjects based on dietary characteristics (MedDietScore, total daily energy intake, percentage of total energy provided by carbohydrates intake), clustered analysis was also performed, particularly the k-means technique. As a measure of distance, the Euclidian distance was used for continuous variables. For the selection of the final number of clusters, the aforementioned methods were used repeatedly, by changing the predetermined number of clusters each time, and the results were analyzed empirically. The decision on the final number of clusters used in our analysis depended on the nature of the data.

Binary logistic regression models were used to evaluate the association between participants' characteristics (i.e., age, sex, BMI, physical activity, cluster of dietary habits, smoking habits, siesta habit) and presence of MetS. Results are expressed as odds ratios and the 95% confidence intervals. Stratified analysis by gender was performed due to suspected interaction between gender and the role of siesta, which was tested after relevant findings in literature. In order to estimate the additive value of each variable entered in the logistic models, a likelihood ratio test for nested models was performed for each variable (26), separately in men and women. The level of statistical significance for interaction terms was set at alpha=0.05 and all statistical tests were performed for 2-tailed hypotheses. Type I error was predefined at 0.05. Statistical analysis was performed in IBM SPSS version 23.0 (Armonk, NY: IBM Corp.).

Results

The overall prevalence of MetS in the study sample was 36.2%, with females being more likely to meet the diagnostic criteria than males (40.0% vs. 31.8%, respectively, p=0.03). Regarding its association with age, MetS was more common among individuals aged between 65 and 80 years old than the very old (i.e., over 80 years old) (38.3% vs. 29.5% respectively, p=0.008). Moreover, subjects who adhered to a Mediterranean diet pattern in the highest tertile were less likely to have MetS as compared subjects with low or moderate adherence to this dietary pattern (29.7% vs. 37.3% respectively, p=0.05). Descriptive characteristics of the study sample, divided in two groups in respect to MetS presence, are summarized in *Table 1*.

Individuals with MetS, when compared to healthy individuals, were more likely to be females (59.2% vs. 51.3% respectively, p=0.003), currently employed in the workforce (38.1% vs. 29.1%, respectively, p=0.050) and with lower educational level as compared to MerS free individuals (2.2% studied for more than 12 school years vs. 6.3%, respectively, p=0.003). Individuals with MetS had significantly higher BMI than healthy subjects (31.20kg/m^2 vs. 27.22 kg/m^2 respectively, p<0.001), were less likely to be physically active (29.7% vs. 39.9% respectively, p=0.001) were less likely to be smokers (10.1% vs. 16.0% respectively, p=0.005) and had dramatically increased prevalence of diabetes (60.3% vs.

0.3%, p<0.001), hypertension (88.7% vs. 61.2%, p<0.001) and hypercholesterolemia (77.3% vs. 41.6%, p<0.001). Moreover, individuals with MetS were more likely to sleep during the day more often than subjects without MetS (89.4% vs. 76.8% respectively, p=0.039) and less likely to reside in a rural area (62.9% vs. 70.8% respectively, p<0.001).

[Table 1]

With respect to dietary patterns, the variables chosen were highly correlated to the physiology of MetS, i.e. daily energy intake, daily amount of carbohydrates and MedDietScore were used as the initial variables to investigate the presence of specific clusters. The 2-means cluster analysis lead to the classification of the individuals into two clusters according to the aforementioned variables (p-values for between clusters variables <0.05). The first cluster represented 37.0% of the participants and was characterized by higher energy intake, high daily percentage of carbohydrates energy and higher MedDietScore named "*Healthy High Carbs diet*", whilst the second cluster represented 63.0% of the participants and was characterized by lower energy intake, a reduction in the amount of total energy obtained from carbohydrates (45.2%, depicting 120±16gr/day) and lower MedDietScore named "*Reduced Carbs diet*". No significant differences were observed between the gender and the cluster membership (p=0.761).

When multivariable binary logistic model was implemented with the presence of MetS as the dependent variable, siesta habit was an independent positive predictor of the presence of MetS (Odds Ratio (OR)=4.049, 95% Confidence Interval (CI): 1.310-12.518) after adjusting for age, gender, smoking status, daily walking time, BMI and dietary cluster membership *(Table 2, Model 1).* Among these parameters, only BMI was an independent predictor of MetS presence (OR per one unit increase=1.166, 95%CI: 1.069-1.272), independently of the same characteristics *(Table 2, Model 1).* Due to suspected interaction between siesta and gender regarding their role in insulin resistance, the interaction term was significant (p=0.05), so the analysis was further stratified by gender *(Table 2, Models 2, 3).*

As predicted, gender had a moderating effect on the role of siesta in MetS presence, but also, the role of dietary cluster differentiated between genders. Specifically, frequent siesta was positively linked to 4-fold higher odds of MetS presence in females (OR=3.43, 95%CI: 1.08-10.9), but not for men (p=0.999). Higher BMI was positively associated with higher odds of MetS presence for both genders (OR=1.87, 95%CI: 1.17-3.00 for males and OR=1.13, 95%CI: 1.03-1.24 for females). Finally, the dietary cluster characterized by reduced carbohydrates as compared to the healthy higher carbohydrates diet was inversely associated with the likelihood of MetS presence, only for men (OR=0.094, 95%CI: 0.010-0.883) but not for women (OR=1.10, 95%CI: 0.424-2.83). Concerning the additive value of the variables in the logistic regression, the addition of BMI was important for both genders, whilst the pattern was totally different for the remaining variables. Only the siesta habit was found to have an important value over BMI (p<0.001), whilst for men, almost every variable apart from siesta had an incremental ability (all p-values <0.05). As regards reduced carbohydrates diet, it was proven to have explanatory ability for MetS, even after being added on top of BMI, smoking, daily walking which were also important variables. However, the addition of siesta did not add any explanatory ability to the final model.

[Table 2]

Discussion

In the present study, the frequent daytime nap called siesta was associated with higher odds of MetS presence only in females, whilst this association was not significant for males. However, a low-carbohydrates dietary cluster was associated with lower odds of MetS presence only among males, but not for females. Moreover, this study confirmed that increased BMI is associated with higher odds of MetS presence in elderly, as well. These findings suggest that the daytime sleeping habit should be treated as a potential indicator of MetS presence among women and the reduced-carbohydrate dietary pattern should be treated as potential indicator of MetS absence among males. Furthermore, this was the first study (to our knowledge) to combine all these lifestyle parameters and the findings suggest the existence of a differentiated MetS expression by gender, warrants further examination.

The important finding concerning the sleeping habits was that siesta was positively associated with higher odds of MetS presence, but only for women, which is in accordance with a previous study finding where the authors reported that the prevalence of MetS was 44.5% among females who had a 0 to 1 napping day siesta, which was significantly higher than the prevalence of MetS among females with no daytime siesta (35.0%, $p<0.001$). In a multi-adjusted analysis, having a siesta for more than one hour was independently associated with an increased prevalence of MetS by 39% as compared to females not having day siesta. The authors also revealed that habitual napping was linked to higher prevalence of central obesity and hypertriglyceridemia and suggested these factors as potential explanations to the pathogenesis or simply be the defining characteristic of MetS associated with siesta. Furthermore, a recent meta-analysis revealed an important J-shape correlation with CVD and the length of siesta (27), but the role of gender was not investigated. In accordance to the present findings, no statistically significant associations were detected between daytime napping and metabolic syndrome among the male subjects (16).

A different trend by gender was also described in the present work for the role of dietary patterns on MetS prevalence. The latter confirmed previous findings, but being associated with different dietary patterns. Specifically, for men, adoption of an "*animal and fried food*" dietary pattern was positively related to MetS presence, whilst for women, the "*high-salt and energy*" dietary pattern was positively related to MetS presence (28). These differences could be related to the different hormonal profile that interacts with glucose-related metabolic parameters. For instance, free testosterone levels and Sex Hormone Binding Globulin levels in women are strongly correlated with MetS presence, a finding that was weakened when it came to analysis in males, with low androgen levels potentially increasing MetS risk (29). Thyroid function, which regulates the most important endocrine pathways, not only is different between males and females, but also recent studies suggests that it affects the risk of developing MetS differently for the two genders (30). The gender differences in insulin resistance regulation could in part be explained by the findings of the present work, where the reduced carbohydrate diet was favourable for men, but was associated with no beneficial effects in women. It should be reminded that gender differences are prone to selection bias as elderly males and females in rural areas of Greece might not have the same access to recruitment for research purposes. However, the participation rates were adequately high to support the presented findings.

As highlighted above, the potential role of modifying lifestyle parameters is of utmost importance when it comes to reduce the burden of MetS, despite the fact that the trends are different influences between males and females. The present study provides new information on the factors associated with MetS in an elderly cohort, as well as on the combined role of lifestyle parameters and their interaction with sex. Moreover, this new information could provide additional information regarding the influences of aspects of the lifestyle treatment approach, by adding the potential for the role of sleeping patterns in the puzzle. Taking into account that dietary and physical activity interventions have already been shown to be successful in treating MetS (31), the addition of sleep interventions could help clinicians to increase the effectiveness of their interventions especially for female subjects and thus, reduce the burden of CVD, which is partially depending on the MetS presence (32).

Limitations

It is important to note that this is a cross-sectional survey and therefore lacks the ability to infer causal relationships. The measurements have been performed once and may be prone to measurement and reporting errors, however this methodology is commonly used worldwide, and this study used validated instruments and suitably qualified and trained staff, making the results comparable to other studies. The sleeping habits have been assessed only in terms of quantity and not quality, which could be equally important, this was employed as the measuring method is easier to implement and could be implemented in routine clinical practice.

Conclusions

Sleeping habits and dietary patterns are strongly associated with the presence of MetS in elderly women, but this association is not seen in elderly men. MetS in women is more linked to sleep than diet, whilst the opposite pattern is prevalent in men. Lifestyle assessment, including quantifying sleep in subjects with existing MetS should become an integral part of clinical practice, especially taking into account that MetS is a CVD risk factor of great significance, but fortunately is modifiable and therefore one that could easily be managed.

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Conflict of interest: None to declare

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Table 1. Lifestyle, psychosocial and clinical characteristics of the MEDIS study participants (*n* = 2749) according to the presence of Metabolic Syndrome (MetS).

	No MetS *(n = 1754)*			MetS *(n = 995)*		
Characteristics	**All**	**Males**	**Females**	**All**	**Males**	**Females**
Gender, men (%)	49.7*	-	-	40.8	-	-
Age (years)	74±7.5	75±7.7	74±7.2	74±6.3	75±6.6	73±6.0
Retired, yes (%)	70.8*	76.1†	65.4	62.9	67.0	60.0
Education: more than 12 years, yes (%)	6.3*	7.4	5.1†	2.2	4.2	0.8
Living in rural area, yes (%)	44.3*	44.0†	44.5†	29.0	30.1	28.2
Living alone, yes (%)	28.5	16.6	41.9	26.5	11.1	38.0
Smoking (current), yes (%)	16.0*	28.2†	3.9	10.1	19.7	3.5
Body Mass Index (kg/m^2)	27.2±4.1*	26.9±3.7†	27.6±4.5†	31.2±4.9	30±4.2	32.0±5.2
Hypercholesterolemia, yes (%)	41.6*	34.1†	48.5†	77.3	69.4	81.5
Hypertension, yes (%)	61.2*	54.1†	59.3†	88.7	80.5	93.1
Diabetes Mellitus, yes (%)	0.3*	0.4†	0.2†	60.3	65.2	56.9
MedDietScore (range 0-55)	33.6±4.1	33±4.4	34±3.9	33.4± 4.0	33±4.2	34±3.8
Physical activity, yes (%)	39.9*	46.3	32.1†	29.7	38.2	23.3
Daily Walking time (minutes)**	60 (20,120)	45(20,120)	60(20,120)	45(15,120)	60(15,98)	40(15,120)
Siesta (afternoon sleep), yes (%)	76.8*	83.3†	71.9†	89.4	93.3	88.2
Reduced Carbs diet, yes (%)	55.7	54.7	56.6	50.8	48.0	52.8

**values are presented as median (25th, 75th percentiles). p-values derived from Student's t-test or non-parametric Mann-Whitney test for non-continuous variables and chi squared test for nominal variables.*p for total sample<0.05, †p for within gender<0.05

Table 2. Multivariable binary logistic regression model for the presence of MetS (*n* = 2749).

	All (*n=2749*)		Males (*n=1369*)		Females (*n=1380*)	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Male vs. female	0.59	0.23-1.49	-	-	-	-
Model 1: Age (per 1 year)	1.01	0.93-1.09	0.89	0.74-3.00	1.05	0.94-1.16
Model 2: *Model 1*+Smoking (yes vs no)	0.64	0.17-2.35	0.69	1.01-1.73*	1.03	0.05-18.3
Model 3: *Model 2*+BMI (per kg/m^2)	1.17	1.07-1.27	1.87	1.17-3.00*	1.13	1.03-1.24*
Model 4a: *Model 3*+Daily walking (per min/day)	1.00	0.99-1.00	0.99	0.98-1.00*	1.00	0.99-1.01
Model 4b: *Model 3*+Physical activity (yes vs. no)	0.84	0.63-1.13	0.80	0.54-1.21	0.87	0.58-1.31
Model 5: *Model 4a*+Reduced CHO diet vs. Healthy High CHO diet	0.69	0.32-1.50	0.09	0.01-0.88*	1.10	0.42-2.83
Model 6: *Model 5*+Siesta (yes vs. no)	4.05	1.31-12.52	2.80	0.31-24.80	3.43	1.08-10.9*

OR: Odds Ratio; CI: Confidence Interval; estimated by binary logistic regression; CHO: Carbohydrates
*Indicates a significant change ($p<0.05$) in -2loglikelihood from the previous (nested) model;

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