CHARLES UNIVERSITY

Faculty of Physical Education and Sport

Extract from doctoral thesis

THE RELATIONSHIP BETWEEN SARCOPENIA AND TWO BEHAVIORAL FACTORS - CIGARETTE SMOKING AND ALCOHOL DRINKING - META-ANALYSIS

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BACKGROUND

Although old age cannot be listed among real diseases, there are many syndromes typical for this part of lifetime. Since the current population has been getting older the understanding of diseases and syndromes connected with old age have become an important objective of scientific studies. The syndromes are mostly characterized by skeletal muscle wasting and physical performance decreasing and they generally lead to frailty. These phenomena usually accompany natural aging; however, they could be accelerated by many factors. It has been known that development of these syndromes is individual and depends on a number of factors. The genetic predispositions are likely to be the main ones and play the primary role. However, we are not able to change them during a lifespan. Another major influence, which is very important, is lifestyle and it could be altered significantly. People during their lifetime can change especially their behavior; they may for example reduce cigarette smoking and alcohol drinking. There have been published some studies in which scientists attempt to find out if there is any relationship between the above mentioned bad habits and low skeletal muscle mass. Some of them suggested a strong relationship (Domiciano et al., 2013; Figueiredo et al., 2013) and some of them indicated only weak relationship (Akune et al., 2014; Atkins, Whincup, Morris, & Wannamethee, 2014; Beavers, Beavers, Serra, Bowden, & Wilson, 2009). Even though there are not any doubts that risk factors do not work independently, it could be interesting to know if cigarette smoking or alcohol drinking as separate risk factors may contribute to decreasing of muscle mass.

Progressive loss of skeletal muscle mass, power and strength were defined by Rosenberg (1989) as sarcopenia. It is a very complex process influenced by a set of elements which contribute to skeletal muscle mass loss (Muscaritoli et al., 2010). They are for example mitochondrial dysfunction, replication defects in mitochondrial DNA that lead to deficit in energy production and muscle fiber atrophy, changes in protein synthesis, imbalance between protein degradation and the ability of muscle fiber to new protein synthesis, changes in secretion and plasmatic levels of hormones (growth hormone, androgens, insulin etc.), metabolic syndrome or imbalance in antioxidant system and many more (Buford et al., 2010). We have been far from being able to fully understand the causes and characteristics of sarcopenia as well as to solve this problem. Sarcopenia treatment and prevention are currently one of the key tasks for scientists who deal with the treatment of diseases accompanying aging of human being. An appropriate

lifestyle with physical activity without smoking and limited alcohol intake seems to be the most effective remedial approach (Morley et al., 2010). In 2010 there was established the European Working Group on Sarcopenia in Older People (EWGSOP). EWGSOP developed a practical clinical definition and consensus diagnostic criteria for age-related sarcopenia (Cruz-Jentoft et al., 2010). The EWGSOP proposals were used as the base instrument for inclusion of the studies into the analyses.

Cigarette smoking should be undoubtedly counted among one of the very serious health risk factors of many diseases. It contributes to development of lung cancer, chronic inflammation and so on. For example, chronic inflammation has been said to be one of the most dangerous risk factors which lead to muscle damaging (Visser et al., 2002; Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000). There are metabolites which are components of the cigarette smoke, these are assumed to be important in sarcopenia development: aldehydes, reactive oxygen species (ROS), and reactive nitrogen species (RNS), they enter the bloodstream and reach the skeletal muscles of smokers and there they accelerate muscle wasting (Rom, Kaisari, Aizenbud, & Reznick, 2012a, 2012b). Nevertheless, it is difficult to say that cigarette smoking itself can directly contribute to sarcopenia.

Alcohol drinking can also be mentioned among health risk factors. Chronic alcohol ingestion may result in many pathological effects, including alcoholic liver disease such as liver inflammation, pancreatic disease, neurological problems, promotion of several forms of cancer, and negative effects on immune function (Forsyth, Voigt, & Keshavarzian, 2014). Ethanol impairs skeletal muscle protein synthesis and muscle autophagy is increased by ethanol exposure that could contribute to sarcopenia (Thapaliya et al., 2014). Alcohol consuming belongs to conditions that have been associated with cachexia due to the alcoholic liver disease (Thomas, 2007). Nevertheless, cachexia is not the same disease as sarcopenia despite being rather similar. In cachexia, pro-inflammatory cytokines have a direct effect on muscle tissue volume, contributing to a loss of muscle mass indistinguishable from sarcopenia. On the other hand, sarcopenia alone has not been shown to contribute to a drop-off in appetite or to loss of fat mass similar to that associated with cachexia (Thomas, 2007).

Although individual studies have depicted that both cigarette smoking and alcohol drinking should be counted among the sarcopenia risk factors (Lee et al., 2007; Thapaliya et al.,

2014), a comparative analysis of those fields has not yet been done, despite the fact that theoretical models of accelerated muscle loss by smoking cigarettes and drinking alcohol have been described in previous research and as it was mentioned above. Since skeletal muscles are an indispensable component of the locomotors system, their changes play an important part in human life. Low muscle mass and sarcopenia are also regarded as a key component of frailty, which is one reason of inadequate self-sufficiency in the elderly. For those reasons a meta-analysis, which could uncover potential relationships between sarcopenia and cigarette smoking or alcohol drinking, may be helpful to prevent sarcopenia and frailty in the future.

OBJECTIVES

The main objectives were to explore relationships between sarcopenia and cigarette smoking and also sarcopenia and alcohol drinking in relatively healthy people over 65 years old on the basis of recommendation of the Cochrane Handbook for Systematic Reviews.

OR between smokers and non-smokers to fall ill with sarcopenia were calculated in the first meta-analysis and OR between alcohol drinkers and non-drinkers were calculated in the second meta-analysis in meta-analyses section of the thesis as the first step.

Additionally, the ORs which were obtained from the individual studies were systematically arranged in the tables and evaluated in the systematic review section as the second step.

Finally, age-adjusted linear regression models were made to find out the comprehensive influence of both variables - the cigarette smoking and alcohol drinking - on development of sarcopenia.

METHODS AND DESIGN

The study was focused on cross-sectional and cohort studies. Almost all of those studies were non-randomized studies. Participants were mostly independent and relatively healthy people over 60 years of age who lived primarily in their own homes or in community-dwelling homes. In two cases there were included patients who were hospitalized in medical care facilities. Data of those patients were used only as additional analyses. The interventions were designed as a retrospective case-control study. Where sarcopenia was considered as the case, cigarette smoking in the first analysis and alcohol drinking in the second analysis represented the exposure. The types of outcome measures were a dichotomous (binary).

The primary outcomes were the sarcopenia status, cigarette smoking and alcohol drinking habits. There was calculated OR as the base of the meta-analyses. OR is a statistical way mostly used for case-control studies to compare frequency of exposure to something in cases and controls. In this case, OR was used to describe quantitatively the association between people exposed to cigarette smoking or alcohol drinking and sarcopenia. For calculating the OR the results of each study were carried over into a 2×2 table giving the numbers of participants who were or were not exposed to the event (cigarette smoking or alcohol drinking) in each of the two groups (sarcopenia and no sarcopenia). There was used the Cochran-Mantel-Haenszel statistical method (Mantel & Haenszel, 1959) and DerSimonian and Laird random-effects model (DerSimonian & Kacker, 2007) for combining results across studies. The I^2 statistic was conducted to find out if heterogeneity was present. Statistics were carried out in the Review Manager 5.3.

A hybrid 8-item instrument was used to identify the quality of articles. The instrument was designed for these analyses and included one item adapted from Bohannon and Glenney (2014) [Participant Inclusion/exclusion criteria explicit]. There was maximum value of 16 points for each study. Furthermore, there were excluded and returned particular studies during the sensitivity analysis to determine the best estimate taking into account the heterogeneity and whether conclusions were sufficiently robust.

Furthermore, the illustrative comparative risks were calculated and they were presented in summary of findings tables. There were 3 main numbers calculated and presented for an outcome in the summary of findings table:

- The relative effect (in that case OR)
- The assumed risk in a group of people who do not suffer from sarcopenia (e.g. baseline risk)
- The corresponding risk in a group of people who do suffer from sarcopenia.

These numbers were based on the meta-analyses of an outcome and the absolute effects across different groups of people at different risks. GRADEprofiler (GRADEpro) was used to create and manage the summary of findings tables.

Moreover, in the systematic review section that was done additionally the tables including OR calculated in some studies were created. Finally, an unstandardized coefficient β was calculated in age-adjusted linear regression model to estimate relation among sarcopenia as a dependent variable and cigarette smoking and alcohol drinking as independent variables. It was made in IMB SPSS Statistics 21.

RESULTS

Of 373 papers identified as potentially relevant by the database searching, twenty were ultimately included in the meta-analyses. **Figure 1** summarizes the yield of the search process. Data of 33,162 participants were analyzed. Among them there were 17,092 males and 16,070 females. Most of them were from North America and none were from Australia. The main characteristics of the included studies are presented in **Table 1**.

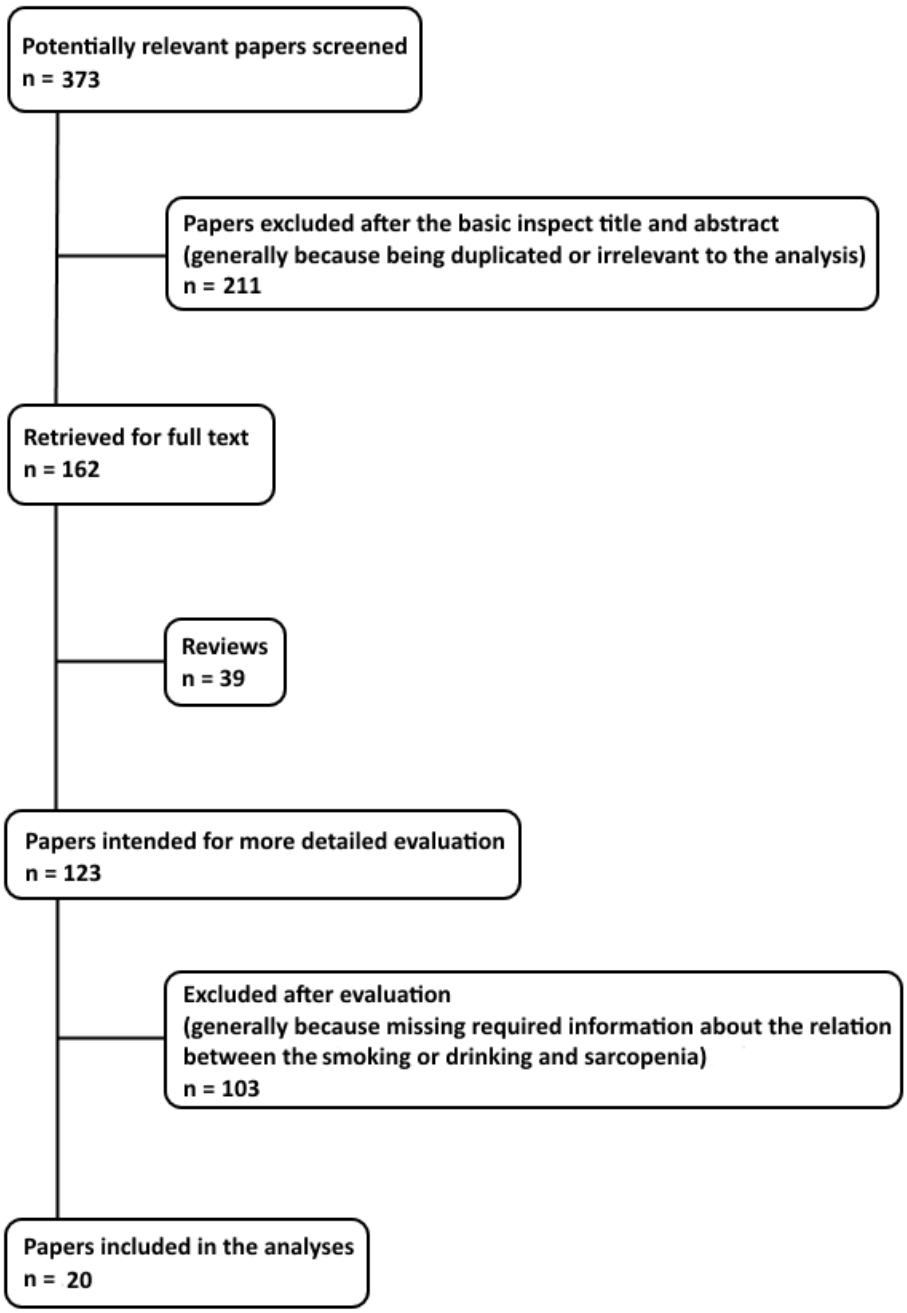

Figure 1 Flow chart indicating how the final sample of papers included in the meta-analyses was established

Table 1 Characteristics of included studies in the meta-analyses

Study Name	Methods	Nationality of Participants	The main aims of study
British Regional Heart Study[1] (Atkins et al., 2014)	A cross-sectional study	British	To explore associations between low muscle mass and a wide range of lifestyle, dietary and cardiovascular risk factors in older men
Chinese Hong Kong (Lau, Lynn, Woo, Kwok, & Melton, 2005)	A cross-sectional study	Chinese	To evaluate the prevalence of and risk factors for sarcopenia in elderly Chinese, and to compare these observations with those in white persons
CRIME Study (Vetrano et al., 2014)	A multicenter observational	Italian	To investigate the association between sarcopenia and mortality during hospital stay and at 1 year after discharge in older individuals admitted to acute care wards
EPIDOS (Rolland et al., 2009)	A cohort study	French	To examine the association of obesity, sarcopenia, and their combination (sarcopenic-obesity) with self-reported difficulties performing physical function
Gariballa and Alessa Study (Gariballa & Alessa, 2013)	A cohort study	United Arab Emirates	To identify the clinical determinants and prognostic significance of sarcopenia in a cohort of hospitalized acutely ill older patients
Health ABC Study[1] (Murphy et al., 2013)	A population-based study	American	To examine the time course of sarcopenia and determinants of transitioning toward and away from sarcopenia
I-Lan Longitudinal Aging Study (Liu et al., 2014)	A cohort study	Taiwanese	To evaluate the prevalence of sarcopenia and its associative clinical characteristics
ilSIRENTE study (Landi et al., 2013)	A cohort study	Italian	To evaluate the impact of sarcopenia on the risk of all-cause death in a population of frail older persons
InCHIANTI (Volpato et al., 2014)	A cross-sectional study	Italian	To estimate the prevalence and investigate the clinical correlates of sarcopenia
KNHANES (Park, Ham, & Lee, 2013)	A cross-sectional study	Koreans	To examine whether vitamin D deficiency was positively associated with sarcopenia in a gender-specific manner in adults aged 50 years, independent of other covariates and possible confounders, including body composition, blood tests, including serum parathyroid hormone (PTH) levels, dietary intake, and hormone replacement therapy in women
KLoSHA[1] (Moon et al., 2010)	A longitudinal study	Koreans	To investigate the effects of subclinical hypothyroidism on the muscle mass, strength or quality in elderly people

Study Name	Methods	Nationality of Participants	The main aims of study
NHANES 1988 – 1994 (Beavers et al., 2009)	A cross-sectional study	American	To test the hypothesis that reduced skeletal muscle index, indicative of sarcopenia, is related to elevation in uric acid
NHANES 1999 – 2004[1] (Goodman et al., 2013)	A validation study	American	To identify predictors of low skeletal muscle mass in older adults toward development of a practical clinical assessment tool for use by clinicians to identify patients requiring dual-energy X-ray absorptiometry (DXA) screening for muscle mass
North District of Taichung City (Lin et al., 2013)	A cross-sectional study	Taiwanese	To determine the prevalence of sarcopenia using the EWGSOP algorithm in a general elderly population in a Taiwanese metropolitan area
Rancho Bernardo Study (Castillo et al., 2003)	A cohort study	American	To examine sarcopenia prevalence and risk factors in community-dwelling men and women who attended a 1988–1992 Rancho Bernardo Study clinic visit
ROAD study (Akune et al., 2013)	A cross-sectional study	Japanese	To investigate the prevalence of sarcopenia using the EWGSOP definition, and clarified the association of sarcopenia with physical performance
SABE Study (Silva Alexandre, Oliveira Duarte, Santos, Wong, & Lebrão, 2013)	A cross-sectional study	Brazilians	To examine the prevalence and factors associated with sarcopenia in older residents in São Paulo, Brazil
SPAH (Domiciano et al., 2013; Figueiredo et al., 2013)	A cohort study	Brazilians	To evaluate the prevalence and risk factors associated with sarcopenia, based on these two criteria
Tianliao Old People study 04 (Wu et al., 2014)	A cross-sectional study	Taiwanese	To show the prevalence and associated factors of sarcopenia and severe sarcopenia in rural community-dwelling older Taiwanese

[1] The study was used only in the systematic review section

Effects of exposures

The OR (95% CI) in cigarette smoking males in the fixed effect model after excluding 2 outliers according to the funnel plot and 1 study according to the quality ratings was 1.65 (1.16 - 2.35), statistically significant The OR (95% CI) in cigarette smoking females in the random effect model after excluding two studies was 1.42 (1.09 - 1.85), statistically significant In cigarette smoking overall population the OR (95% CI) in the random effect model after excluding 4 outliers and 2 studies according to the quality ratings was 1.38 (1.15 - 1.66), statistically significant. There was not heterogeneity according to I^2, which was 0% in all cases.

The OR (95% CI) in alcohol drinking males in both models had the same value 0.67 (0.54 - 0.83), both statistically significant. The OR (95% CI) in alcohol drinking females in the fixed effect model after excluding 1 outlier and 1 study was 0.89 (0.73 - 1.08), not statistically significant, moreover, the test for the overall effect was very low level. In alcohol drinking overall population the OR (95% CI) in fixed effect model after excluding 1 outlier was 0.77 (0.67 - 0.88). There also was not heterogeneity according to I^2, which was 0% in all cases. All the analyses of alcohol drinking were more robust than the analyses of cigarette smoking. Moreover, except the random effect model after excluding 1 study in alcohol drinking females (OR 1.00 (0.75 - 1.34)) all the OR were below 1.

Summary of the outcomes

The outcomes of the meta-analyses are presented in the following sequence - the cigarette smoking males (**Figure 2**), cigarette smoking females (**Figure 3**), cigarette smoking overall population (**Figure 4**), and overall population including hospitalized patients (**Figure 5**), and alcohol drinking males (**Figure 6**), alcohol drinking females (**Figure 7**), alcohol drinking overall population (**Figure 8**), and overall population including hospitalized patients (**Figure 9**). The outcomes were considered to be those that had higher level in the test for the overall effect. In all the analyses the more robust model was chosen out of two possible solutions - the fixed effect model and the random effect model.

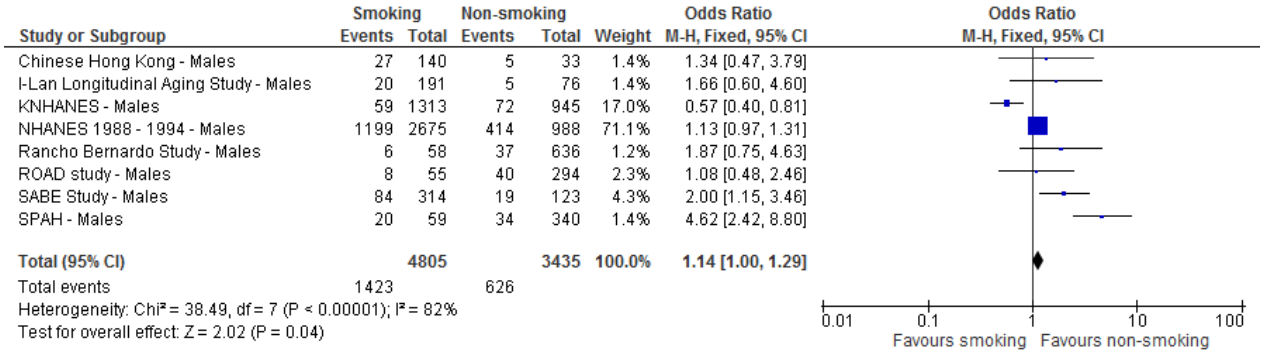

Figure 2 The cigarette smoking males' meta-analysis

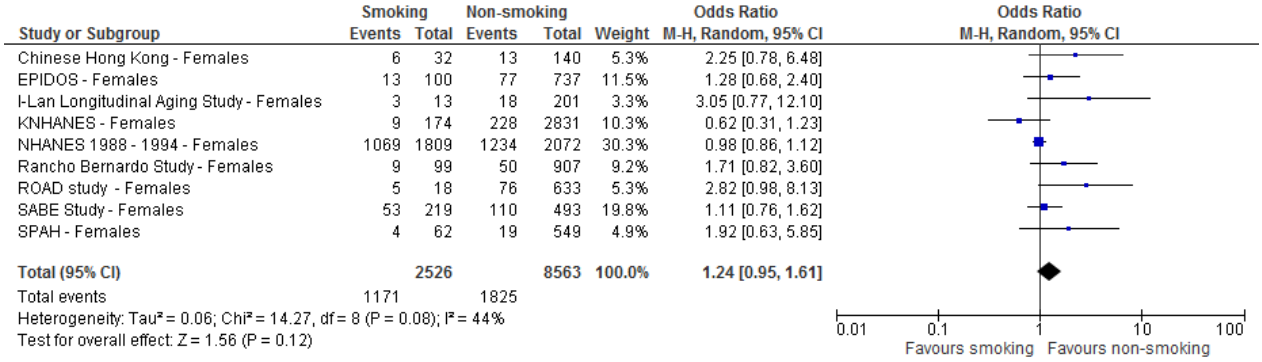

Figure 3 The cigarette smoking females' meta-analysis

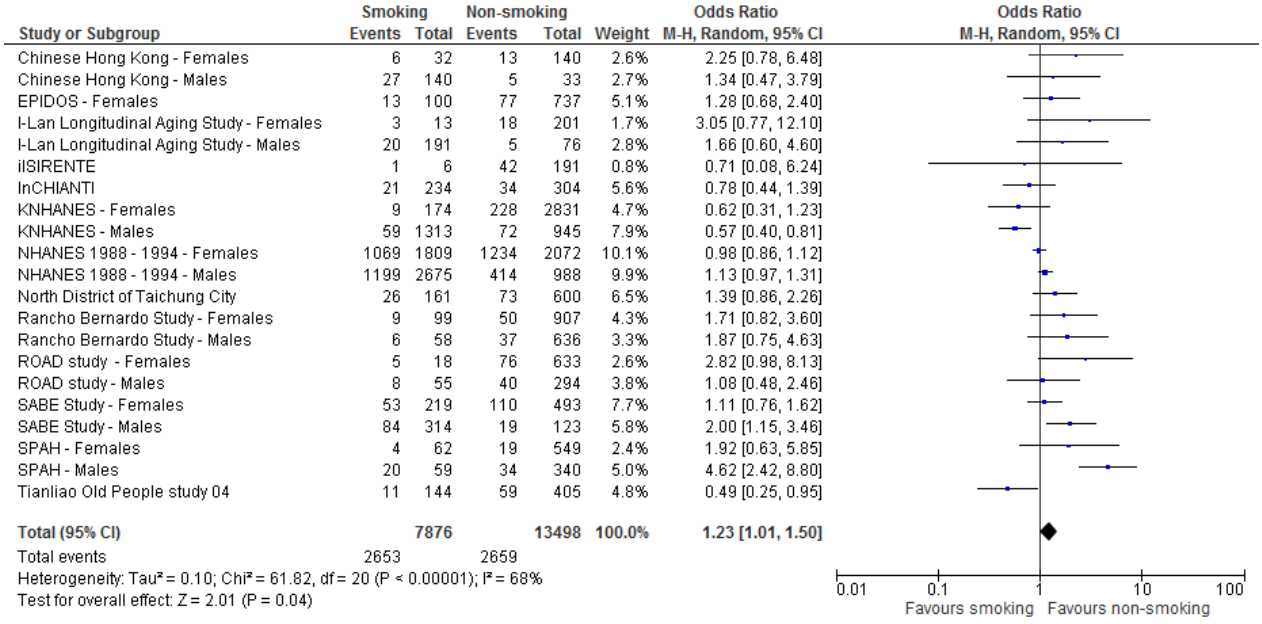

Figure 4 The cigarette smoking overall population meta-analysis

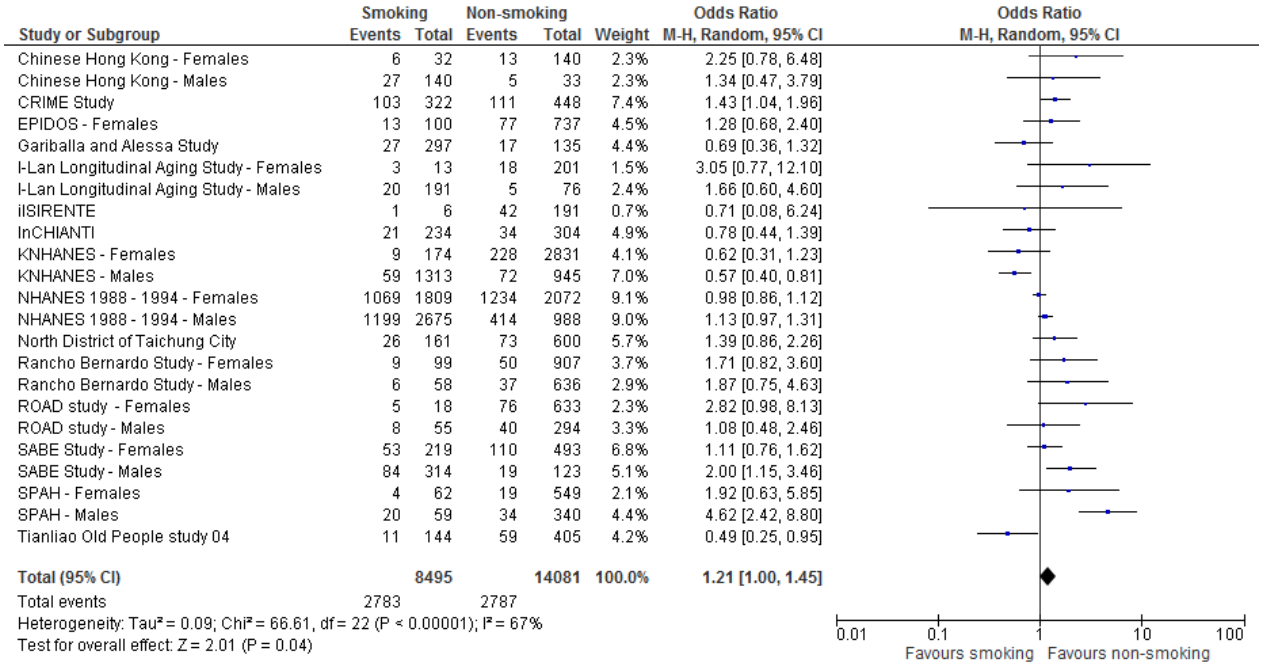

Figure 5 The cigarette smoking overall population including hospitalized patients meta-analysis

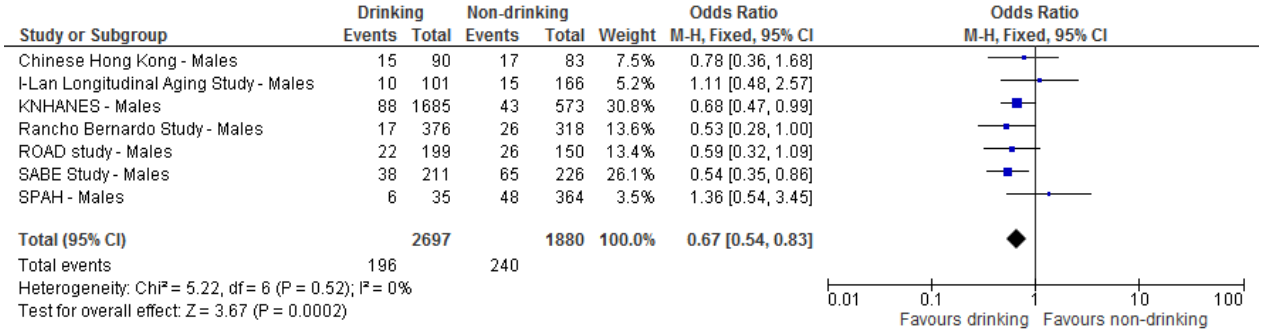

Figure 6 The alcohol drinking males' meta-analysis

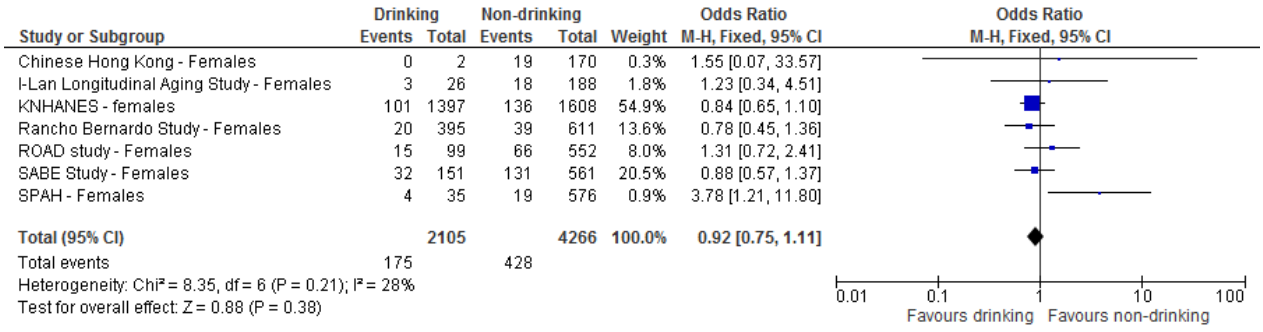

Figure 7 The alcohol drinking females' meta-analysis

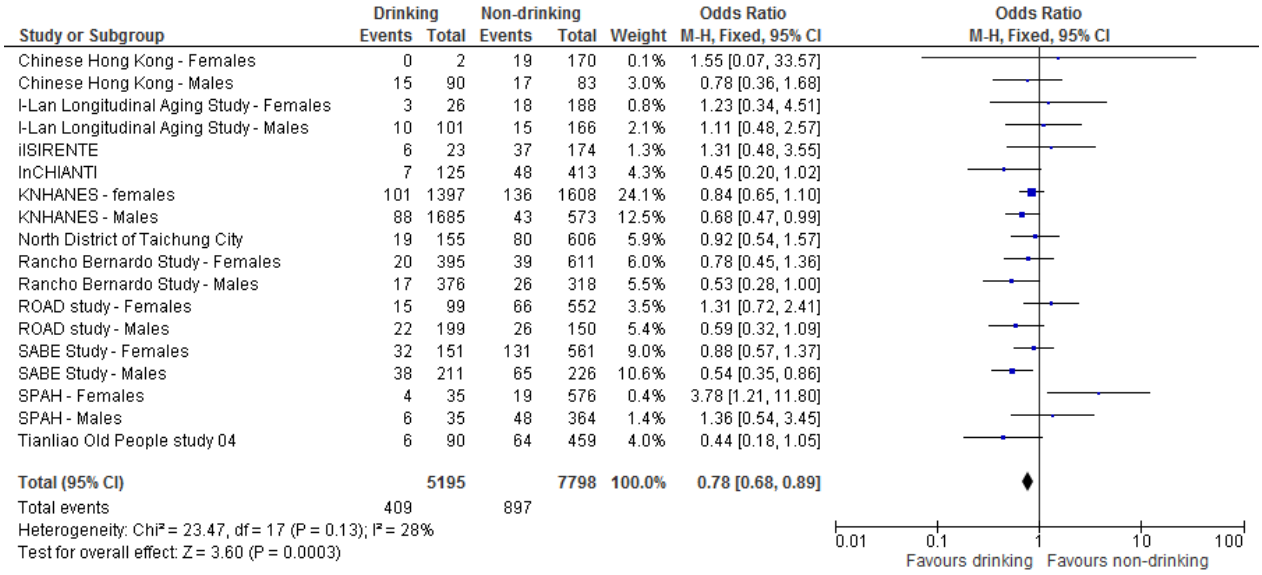

Figure 8 The alcohol drinking overall population' meta-analysis

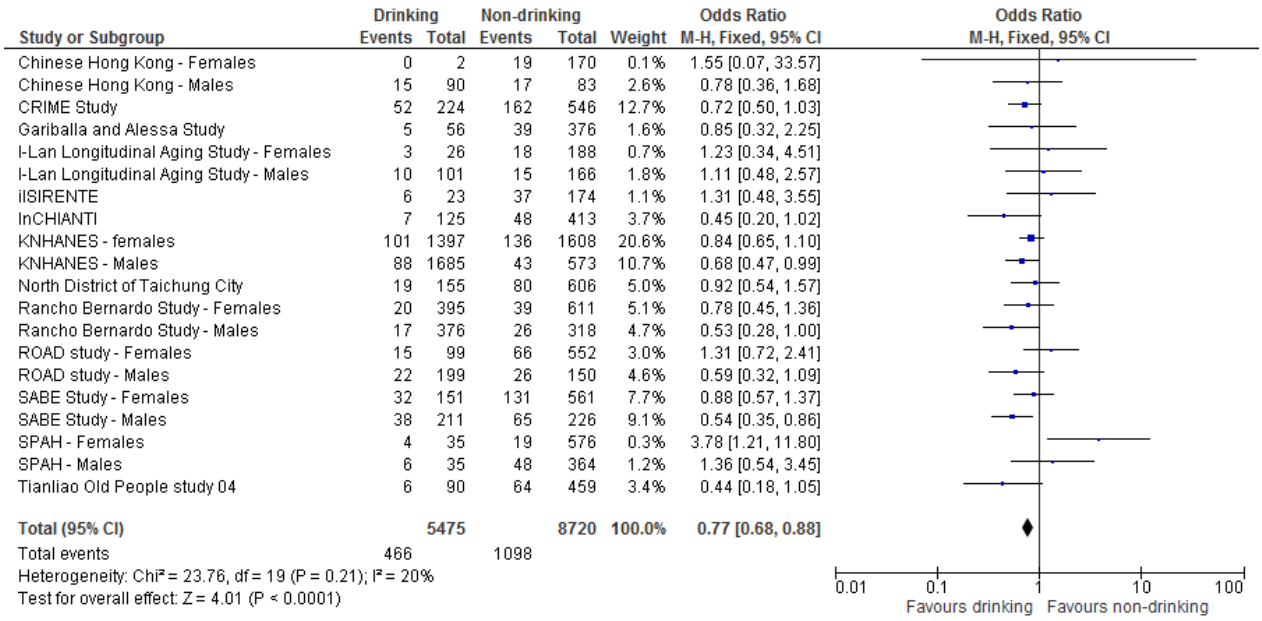

Figure 9 The alcohol drinking overall population with hospitalized patients' meta-analysis

Summary of findings table

There were used optimal ORs according to the sensitivity analyses to create the summary of finding table.

The assumed risk in the non-smoking males group was 91 per 1,000 and the corresponding risk in the smoking males group was 142 per 1,000 (95% CI 104 to 191) which meant that there was statistically significantly higher number of males suffering from sarcopenia in the cigarette smoking group. The corresponding risk in medium risk population was 181 per 1,000 (95% CI 134 to 239).

The assumed risk in the non-smoking females group was 99 per 1,000 and the corresponding risk in the smoking females group was 135 per 1,000 (95% CI 107 to 169). There was also statistically significant higher number of females suffering from sarcopenia in the cigarette smoking group. The corresponding risk in medium risk population was 127 per 1,000 (95% CI 101 to 159).

Finally, the assumed risk in the non-smoking overall population was 104 per 1,000 and the corresponding risk there was 139 per 1,000 (95% CI 118 to 162). A higher number of people who were suffering from sarcopenia was also in the cigarette smoking group and that was also statistically significant. The corresponding risk was 148 per 1,000 (95% CI 127 to 173) in medium risk population.

Those analyses confirmed that cigarette smoking could accelerate sarcopenia development. However, the quality of the evidence was very low in all the cases mainly due to the fact that most studies were non-randomized cross-sectional studies with high risk of bias. The summary of findings table of the cigarette smoking meta-analyses is shown in **Table 2**.

Table 2 Summary of findings table of cigarette smoking meta-analyses

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Non-smoking	**Smoking**			
Males	**Study population**[1]		**OR 1.65** (1.16 to 2.35)	1920 (5)	⊕⊖⊖⊖ **very low**[4]
	91 per 1000	**142 per 1000** (104 to 191)			
	Medium risk population[2,3]				
	118 per 1000	**181 per 1000** (134 to 239)			
Females	**Study population**[1]		**OR 1.42** (1.09 to 1.85)	4203 (7)	⊕⊖⊖⊖ **very low**[4]
	99 per 1000	**135 per 1000** (107 to 169)			
	Medium risk population[2,3]				
	93 per 1000	**127 per 1000** (101 to 159)			
Overall population	**Study population**[1]		**OR 1.38** (1.15 to 1.66)	7619 (15)	⊕⊖⊖⊖ **very low**[4]
	104 per 1000	**139 per 1000** (118 to 162)			
	Medium risk population[2,3]				
	112 per 1000	**148 per 1000** (127 to 173)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the exposition (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

[1] The numbers of people suffering from sarcopenia in the analyzed groups per 1000 participants

[2] The basis for the assumed risk is the median control group risk across studies

[3] The median control group risk across studies was calculated, because there was relatively little variation in the baseline risks across the studies included in the meta-analysis

[4] Most studies were non-randomized cross-sectional studies with risk of bias

There also were used optimal ORs according to the sensitivity analyses to create all of the summaries of the finding table. Nevertheless, the OR in the males was the only one which included all the studies.

The assumed risk in the non-drinking males group was 128 per 1,000 and the corresponding risk in the drinking males group was 89 per 1,000 (95% CI 73 to 108). The corresponding risk in medium risk population was 92 per 1,000 (95% CI 76 to 112).

The assumed risk in the non-drinking females group was 111 per 1,000 and the corresponding risk in the drinking females group was 100 per 1,000 (95% CI 83 to 120). The corresponding risk in medium risk population was 86 per 1,000 (95% CI 72 to 104).

The assumed risk in the non-drinking overall population was 122 per 1,000 and the corresponding risk there was 96 per 1,000 (95% CI 85 to 109). The corresponding risk was 93 per 1,000 (95% CI 82 to 105) in medium risk population.

A higher number of people who were suffering from sarcopenia was always in the non-drinking group and that except in females analysis was statistically significant. Those analyses did not confirm that alcohol drinking could accelerate sarcopenia development; quite the opposite. However, the quality of the evidence was also very low in all the cases. Therefore there were most studies non-randomized cross-sectional studies with high risk of bias. The summary of findings table of the alcohol drinking meta-analyses is shown in **Table 3**.

Systematic review section

The ORs with cigarette smoking as the main variable in the regression models varied from 0.73 (0.34 - 1.58) to 3.44 (1.18 - 9.96) in the males, from 1.88 (1.06 - 3.32) to 2.93 (0.47 - 18.36) in the females and from 0.55 (0.27 - 1.15) to 2.03 (0.86 - 4.78) in the overall population. Nevertheless, almost all the ORs were above 1, which denoted that cigarette smoking as a variable could be counted among sarcopenia risk factors. The relationship between sarcopenia and cigarette smoking according to regression models is shown in **Tables 4** and **5**.

Table 3 Summary of findings table of the alcohol drinking meta-analyses

	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Non-drinking	**Drinking**			
Males	**Study population**[1]		**OR 0.67** (0.54 to 0.83)	4577 (7)	⊕⊖⊖⊖ **very low**[4]
	128 per 1000	**89 per 1000** (73 to 108)			
	Medium risk population[2,3]				
	132 per 1000	**92 per 1000** (76 to 112)			
Females	**Study population**[1]		**OR 0.89** (0.73 to 1.09)	5588 (5)	⊕⊖⊖⊖ **very low**[4]
	111 per 1000	**100 per 1000** (83 to 120)			
	Medium risk population[2,3]				
	96 per 1000	**86 per 1000** (72 to 104)			
Overall population	**Study population**[1]		**OR 0.77** (0.67 to 0.88)	12382 (17)	⊕⊖⊖⊖ **very low**[4]
	122 per 1000	**96 per 1000** (85 to 109)			
	Medium risk population[2,3]				
	118 per 1000	**93 per 1000** (82 to 105)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the exposition (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio

[1] The numbers of people suffering from sarcopenia in the analyzed groups per 1000 participants

[2] The basis for the assumed risk is the median control group risk across studies

[3] The median control group risk across studies was calculated, because there was relatively little variation in the baseline risks across the studies included in the meta-analysis

[4] Most studies were non-randomized cross-sectional studies with risk of bias

In comparison with cigarette smoking regression models there was not such huge difference among resulting ORs in the alcohol drinking regression models. The OR with alcohol drinking as the main variable in regression models varied from 0.56 (0.29 - 1.10) to 1.33 (0.74 - 1.20) in males, from 0.87 (0.48 - 1.54) to 1.33 (0.90 - 1.98) and finally from 0.88 (0.40 - 1.95) to

1.14 (0.45 - 2.91) in overall population. In the males all the ORs except one were below 1, which could mean that alcohol drinking did not make sarcopenia development worse. The rest is oscillated about 1, thus there could be confirmed that alcohol drinking did not intensify sarcopenia progress (**Table 6** and **7**).

Table 4 The systematic review of relation between sarcopenia and cigarette smoking, according to multiple regression models

Study name	Multiple logistic regression models	Status	OR (95 % CI)
I-Lan Longitudinal Aging Study - overall population	Univariate	Past vs. never Present vs. never	0.55 (0.22 - 1.34)[1] 0.55 (0.27 - 1.15)[1]
NHANES 1999 – 2004 males	Adjusted for age, race, marital status, educational level, BMI, total cholesterol, blood pressure, high-density lipoprotein, alcohol, morbidity	Current smoker vs. no	0.73 (0.34 - 1.58)
Tianliao Old People study 04 - overall population	Adjusted for age, Waist circumference, sex, BMI, working regularly, alcohol drinking, Mini-Nutritional Assessment score, history of hypertension, history of diabetes, SPPB score†, SPMSQ Score‡	Yes vs. no	0.87 (0.34 - 2.22)
British Regional Heart Study - males	Adjusted for age, BMI, physical activity, alcohol, social class, morbidity (CVD, diabetes, cancer, FEV1, poor/fair health)	Current smoker	0.94 (0.73 - 1.22)
NHANES 1999 – 2004 males	Unadjusted	Current smoker vs. no	0.94 (0.70 - 1.91)
Health ABC Study overall population	Unclear	Former vs. never	0.96 (0.79 - 1.15)
Health ABC Study overall population	Unclear	Current vs. never	1.07 (0.78 - 1.48)
NHANES 1988 – 1994 overall population	Adjusted for age, BMI, protein intake, serum uric acid	Current vs. never	1.1 (0.9 - 1.5)
SABE Study overall population	Adjusted for age, sex, marital status, lifestyle, Mini Mental State exam, risk for undernutrition	Former vs. never	1.16 (0.76 - 1.78)
North District of Taichung City - overall population	Adjusted for age, sex, marital status, regular exercise habits, comorbidity status	Former vs. never	1.18 (0.56 - 2.49)
Chinese Hong Kong males	Adjusted for age	Current or ex-smoker vs. never	1.2 (0.4 - 3.4)
NHANES 1988 – 1994 overall population	Adjusted for age, BMI, protein intake, serum uric acid	Former vs. never	1.3 (1.1 - 1.6)*
ROAD study - males	Adjusted for age and BMI	Yes vs. no	1.49 (0.59 - 3.75)
KLoSHA - males	Adjusted for age, alcohol, history of diabetes, hypertension, and acute coronary event, LDL-cholesterol, leg fat free mass, physical activity score, the presence of knee pain, physical activity score	Yes vs. no	1.76 (0.79 - 3.90)
ROAD study overall population	Adjusted for age, sex, and BMI	Yes vs. no	1.86 (0.86 - 4.02)
NHANES 1999 – 2004 females	Adjusted for age, race, married status, educational level, BMI, total cholesterol, blood pressure, high-density lipoprotein, alcohol, morbidity	Current smoker vs. no	1.88 (1.06 - 3.32)*
Rancho Bernardo Study females	Adjusted for age, exercise, alcohol	Current vs. not current	1.90 (0.83 - 4.34)

*statistically significant
† Short physical performance battery
‡ Short portable mental status questionnaire
OR: Odds ratio; **CI:** Confidence interval

OR below 1 means that cigarette smoking as one of variables could have a protective influence against sarcopenia
OR above 1 means that cigarette smoking as one of variables could make worse sarcopenia
[1]There is not certain if results are interpreted well, probably authors of study could have changed variables

Table 5 The systematic review of relation between sarcopenia and cigarette smoking, according to multiple regression models the second part

Study name	Multiple logistic regression models	Status	OR (95 % CI)
SABE Study overall population	Adjusted for age, sex, marital status, lifestyle, Mini Mental State exam, risk for undernutrition	Current vs. never	2.00 (1.11 - 3.63)*
North District of Taichung City - overall population	Adjusted for age, sex, marital status, regular exercise habits, comorbidity status	Current vs. never	2.03 (0.86 - 4.78)
Chinese Hong Kong females	Adjusted for age	Current or ex-smoker vs. never	2.4 (0.8 - 6.9)
NHANES 1999 – 2004 females	Unadjusted	Current smoker vs. no	2.40 (1.69 - 3.41)*
ROAD study - females	Adjusted for age and BMI	Yes vs. no	2.44 (0.61 - 9.72)
Rancho Bernardo Study males	Adjusted for age, exercise, alcohol	Current vs. not current	2.46 (0.87 - 7.00)
KLoSHA - females	Adjusted for age, alcohol, history of diabetes, hypertension, and acute coronary event, LDL-cholesterol, leg fat free mass, physical activity score, the presence of knee pain, physical activity score	Yes vs. no	2.93 (0.47 - 18.36)
SPAH - males	Adjusted for age, BMI, race, physical activity, total femur bone mineral density	Current smoker	3.44 (1.18 - 9.96)*

*statistically significant
OR: Odds ratio; **CI:** Confidence interval

OR above 2 means really strong influence of cigarette smoking as one of variables on a sarcopenia development

Table 6 The systematic review of relation between sarcopenia and alcohol drinking, according to multiple regression models

Study name	Multiple logistic regression models	Status	OR (95 % CI)
Rancho Bernardo Study males	Adjusted for age, exercise, smoking	Heavy vs. not heavy	0.56 (0.29 - 1.10)
KLoSHA - males	Adjusted for age, smoking, history of diabetes, hypertension, and acute coronary event, LDL-cholesterol, leg fat free mass, physical activity score, the presence of knee pain, physical activity score	Yes vs. no	0.63 (0.28 - 1.41)
Chinese Hong Kong males	Adjusted for age	<7 days/wk. vs. never daily vs. never	0.7 (0.3 - 1.8) 0.7 (0.3 - 1.9)
NHANES 1999 – 2004 males	Unadjusted	Alcohol use vs. no	0.71 (0.50 - 1.02)
NHANES 1999 – 2004 females	Unadjusted	Alcohol use vs. no	0.75 (0.59 - 0.96)*
ROAD study males	Adjusted for age and BMI	Yes vs. no	0.78 (0.40 - 1.53)
British Regional Heart Study - males	Adjusted for age, BMI, smoking, physical activity, social class, morbidity (CVD, diabetes, cancer, FEV1, poor/fair health)	Heavy drinker	0.80 (0.47 - 1.36)
Rancho Bernardo Study females	Adjusted for age, exercise, smoking	Heavy vs. not heavy	0.87 (0.48 - 1.54)
North District of Taichung City - overall population	Adjusted for age, sex, marital status, regular exercise habits, comorbidity status	Current vs. never	0.88 (0.40 - 1.95)
ROAD study overall population	Adjusted for age, sex, and BMI	Yes vs. no	1.00 (0.60 - 1.67)

*statistically significant
OR: Odds ratio; **CI:** Confidence interval

OR below 1 means that alcohol drinking as one of variables could have a protective influence against sarcopenia

Table 7 The systematic review of relation between sarcopenia and alcohol drinking, according to multiple regression models the second part

Study name	Multiple logistic regression models	Status	OR (95 % CI)
KLoSHA - females	Adjusted for age, smoking, history of diabetes, hypertension, and acute coronary event, LDL-cholesterol, leg fat free mass, physical activity score, the presence of knee pain, physical activity score	Yes vs. no	1.01 (0.19 - 5.47)
Tianliao Old People study 04 - overall population	Adjusted for age, Waist circumference, sex, BMI, working regularly, habitual smoking, Mini-Nutritional Assessment score, history of hypertension, history of diabetes, SPPB score[†], SPMSQ Score[‡]	Yes vs. no	1.06 (0.39 - 2.86)
North District of Taichung City - overall population	Adjusted for age, sex, marital status, regular exercise habits, comorbidity status	Former vs. never	1.14 (0.45 - 2.91)
ROAD study females	Adjusted for age and BMI	Yes vs. no	1.26 (0.58 - 2.71)
NHANES 1999 – 2004 males	Adjusted for age, race, marital status, educational level, BMI, total cholesterol, blood pressure, high-density lipoprotein, smoking, morbidity	Alcohol use vs. no	1.33 (0.74 - 1.20)
NHANES 1999 – 2004 females	Adjusted for age, race, married status, educational level, BMI, total cholesterol, blood pressure, high-density lipoprotein, smoking, morbidity	Alcohol use vs. no	1.33 (0.90 - 1.98)

OR: Odds ratio; **CI:** Confidence interval

OR above 1 means that alcohol drinking as one of variables could make worse sarcopenia

Multiple regression analysis

In that analysis there was studied whether cigarette smoking and alcohol drinking relate with prevalence of sarcopenia in age-adjusted linear regression models. The unstandardized coefficient *B* was statistically significant only in two cases; it was in the smoking males (0.212) and the smoking overall population (0.153). Since the both unstandardized coefficients *B* had positive values, there could be concluded that increasing of smoking percentage caused the increasing of sarcopenia prevalence. The unstandardized coefficient *B* was very near of statistically significant level at $p<0.05$ in the variable age in the males group, where the unstandardized coefficient *B* was 0.907, which meant that every year of aging might increase sarcopenia prevalence by about 1 point. The test power was the strongest in the males analysis (adjusted $R^2 = 0.736$). In contrast of the males analysis, the females regression model was very weak (adjusted $R^2 = 0.087$). The test power in the overall population was also relatively weak,

nevertheless, it was stronger than in the females (adjusted R^2 = 0.265). The results of the linear regression models are presented in **Table 8**.

Table 8 Associations of selected factors with sarcopenia in linear regression models

Variables	Males			Females			All		
	B	SE	*p* value	*B*	SE	*p* value	*B*	SE	*p* value
Age (years)	0.907[1]	0.317	0.065	-0.245	0.536	0.679	0.416	0.259	0.129
Smoking (%)	0.212[2]	0.055	0.030*	0.528	0.295	0.172	0.153	0.066	0.034*
Drinking (%)	-0.103[3]	0.090	0.335	-0.084	0.197	0.697	-0.070	0.093	0.465
	Adjusted R^2 = 0.736			Adjusted R^2 = 0.087			Adjusted R^2 = 0.265		

B = Unstandardized coefficient
* statistically significant at p<0.05

[1] It means when people get older by about 1 year the sarcopenia prevalence increases by this value approx.
[2] It means when percentage of smokers increases by about 1 point the sarcopenia prevalence increases by this value approx.
[3] It means when percentage of drinkers increases by about 1 point the sarcopenia prevalence decreases by this value approx.

DISCUSSION

The results of the meta-analyses partly confirmed that cigarette smoking rather than alcohol drinking could contribute to sarcopenia development. However, what was really found out? The number of cigarette smoking people was higher in sarcopenia group in all the studies in contrast to the number of alcohol drinking people. There it was the opposite. On the basis of those numbers there were calculated the ORs, which were also due to the sensitivity analysis almost all statistically significant. Although the results could be confirmed as satisfactory there were relatively many problems which the meta-analysis uncovered. It was mainly huge ambiguities in scientific approaches across the studies. For example, it was sarcopenia diagnosing. Since sarcopenia was defined so broadly there have been developed many methods for its diagnosing. Various methods of sarcopenia diagnosing were studied by the author of the thesis and they are extensively descripted in the papers in appendixes. Currently the EWGSOP algorithm which was proposed in 2010 (Cruz-Jentoft et al., 2010) has been considered as the best tool for sarcopenia diagnosing. Also, there for the purposes of the meta-analyses, the EWGSOP

algorithm and muscle mass measurement by DEXA or BIA were chosen as suitable methods of sarcopenia diagnosis. However, the reference values should be unified. As there were used different values as cut off points of ASM or SMI in the observed studies, the prevalence of sarcopenia significantly varied. Basically, there was used almost a special value of ASM and SMI in every study. For example, as the cut off point for males there was used ASM/height^2 < 5.72 kg/m^2 in the Chinese Hong Kong (Lau et al., 2005) and much bigger value (< 7.0 kg/m2) was used in the I-Lan Longitudinal Aging Study (Liu et al., 2014), or < 4.82 kg/m^2 was used as cut off point for females in the Chinese Hong Kong (Lau et al., 2005) and < 5.9 kg/m^2 was used in the I-Lan Longitudinal Aging Study (Liu et al., 2014). All of those values were measured by DEXA. Also values measured by BIA varied considerably. The SMI cut off points for males began from < 7.0 kg/m^2 in the ROAD study (Akune et al., 2013) to < 8.87 kg/m^2 in CRIME Study (Vetrano et al., 2014) and for females from < 5.67 kg/m^2 in the Tianliao Old People study 04 (Wu et al., 2014) to < 6.42 kg/m^2 in the CRIME Study (Vetrano et al., 2014). Those cut off points were established on the basis of the proposal to be the 2 standard deviations or more below the sex-specific average for young adults. Nevertheless, were those values justified? Were the elderly really connected with young adults as regards muscle mass? Indeed, they each had their own life history. It is hard to say that the above mentioned problems significantly contributed to the huge variance of sarcopenia prevalence across the observed studies or if there played more important role other unknown factors. Nevertheless, sarcopenia prevalence only 3.8% in 74 years old females in the SPAH (Domiciano et al., 2013) would seem to be definitely low mainly comparing with 59.3% sarcopenia prevalence in the NHANES 1988 – 1994 (Beavers et al., 2009).

The ascertainment of exposure was another problem which might be improved. There was almost impossible to find more precise data such as a total number of smoked cigarettes or alcohol units. Exposure status was divided into a number of categories according to the daily amount, exposure period in the subjects' lifetimes or current habits. Therefore, it was difficult in this work to find and establish an optimal combination of categories. Different methods to quantify the status were applied almost in every study. In any event, all approaches were based on the subjective evaluation of the participants. Although self-reports are more reliable and valid than it is sometimes supposed, they can be influenced by deliberate under- or overestimation of consumption and by failures of memory and other cognitive factors (Babor, Steinberg, Anton, &

Del Boca, 2000). Probably the proposal of ascertainment method which is not based on the subjective evaluation of participants may be hardly established for clinical needs. Nevertheless, some suitable methods have been created previously. They are for example the smoking pack-years for smoking status (Masters & Tutt, 2007) and the alcohol use disorders identification test (AUDIT) (Babor, Higgins-Biddle, Saunders, & Monteiro, 2001), following the recommendations of the World Health Organization (WHO). Anyway, the subjective component of ascertainment probably played the negative role in the huge variability of percentage of cigarette smokers and alcohol drinkers among the individual studies. It was really hard to believe that among the 172 females in the Chinese Hong Kong (Lau et al., 2005) were only 1.2% alcohol drinkers or that among the 197 participants in the ilSIRENTE study (Landi et al., 2013) were only 3% smokers or that 80.9% among 173 males in the Chinese Hong Kong (Lau et al., 2005) were smokers. The big variability was among all the studies in both statuses; this fact could have had an important impact on the results.

Besides the problems with sarcopenia diagnosing and the ascertainment of exposure there was detected statistically significant age-difference between sarcopenia and no sarcopenia group. That difference could work as important undesirable influence affecting the results. It has been known aging plays significant role in sarcopenia development, because a human organism could be changed by aging after getting seventy years very quickly. The age-difference more than 5 years was found in some studies which were analyzed. For example it was in the I-Lan Longitudinal Aging (Liu et al., 2014) and the SABE Study (Silva Alexandre et al., 2014) in males, in the ROAD study (Akune et al., 2013) and the SABE Study (Silva Alexandre et al., 2014) in females and in the InCHIANTI (Volpato et al., 2013) and the Tianliao Old People study 04 (Wu et al., 2014) in the overall population. Some questions came into existence due to the age-difference in groups. For example, there were significantly more alcohol drinkers in non-sarcopenia group; nevertheless, participants in that group were significantly younger, then how many drinkers from the no sarcopenia group would die perhaps due to alcohol drinking before they could reach the same age as the participants in the sarcopenia group? On the other hand, the more cigarette smoking individuals were in the older group where participants were suffering from sarcopenia, then could not the cigarette smoking have a protective influence and smokers could live longer? These questions are just hypothetical and rhetorical and answering them was not the aim of the study.

Except the above mentioned shortcomings in the study protocols there has to be mentioned that there was not a study where the main aim was neither to explore the relationship between sarcopenia and cigarette smoking nor alcohol drinking alone. Those bad habits always were a part of a cluster of observed variables. Then the exclusion and inclusion criteria were constructed according to the individual study protocols and data of some participants which could be interesting to explore, was missed. A lot diversity of exclusion criteria was used, for example the previous history of hip fracture or hip replacement, unable to walk independently, to understand and answer the questionnaire in the EPIDOS (Rolland et al., 2009); a poor function status, which could lead to a fail in evaluation, such as unable to complete a 6-m timed walk within a reasonable period of time, an implant that was contraindicated for magnetic resonance imaging in the I-Lan Longitudinal Aging Study (Liu et al., 2014); leg edema, pacemaker, joint prosthesis, severe varicosities in the InCHIANTI study (Volpato et al., 2013); individuals who answered yes for the question "Do you currently have kidney failure?" because the kidney plays an important role in vitamin D action in the KNHANES (Park et al., 2014); unable to perform the handgrip strength test or the walking portion of the Short Physical Performance battery, or unable to stand for measurement of weight and height in the SABE Study (Silva Alexandre et al., 2014) and so on. Some of these kinds of criteria would not be necessary in the event that the main aim of study was just the relation between sarcopenia and cigarette smoking or alcohol drinking. There were thus for instance excluded subjects who were older, had less education, drank less, reported more difficulties in activities of daily living and instrumental activities of daily living, more hypertension, diabetes, lung disease, heart disease, stroke, falls, instances of hospitalization, more sedentary lifestyle, more cognitive impairment, undernutrition and risk for undernutrition according to the Mini-nutritional assessment in the SABE Study (Silva Alexandre et al., 2014). Nevertheless, the inclusion of those subjects in the meta-analysis could slightly tangle the results. In contrast, exclusion criteria were not used in the ROAD study (Akune et al., 2013), Rancho Bernardo Study (Castillo et al., 2003), NHANES 1988 – 1994 (Beavers et al., 2009), ilSIRENTE study (Landi et al., 2013) and Chinese Hong Kong (Lau et al., 2005). All the data from the studies were clustered into the meta-analyses without regard to the fact if participants were accepted according to the same exclusion and inclusion criteria. Therefore, the cluster of the included studies could bring a little bit different results if the criteria were the same for all of those.

To sum up, there was found out that cigarette smoking might make sarcopenia prognosis worse, thus the findings confirmed the conclusions that have been published previously (Chang et al., 2012; Lee et al., 2007; Rom et al., 2012a, 2012b; Rom, Kaisari, Aizenbud, & Reznick, 2013; Szulc, Duboeuf, Marchand, & Delmas, 2004). In contrast, alcohol drinking was not detected as the risk factor contributing to development of sarcopenia, even more according to the results of alcohol drinking meta-analyses the alcohol drinking could have protective character against sarcopenia. Nevertheless, Boffetta and Garfinkel (1990) came to very similar findings about mortality and coronary heart disease (CHD). There the moderate alcohol intake had also a protective effect on CHD mortality. Notwithstanding, the other authors partly confirmed the possible protective influence of alcohol drinking on CHD mortality (Kannel & Ellison, 1996), it is important to be sure that advice that encourages the public to drink to avoid any diseases such as CHD or sarcopenia does not increase abuse. However, the above mentioned problems with sarcopenia diagnosing, ascertainment of exposure and age-differentness probably contributed to considerable heterogeneity in almost all the analyses. Moreover, if there is added the high risk of bias due to non-randomized design of the studies, almost all the results had low significance which could hardly be globalized. Therefore, there is a need to do other analyses to confirm the results of this study.

AUTHOR CONCLUSIONS

Implications for practice

According to the results of this study there would be recommended to restrict cigarette smoking to prevent sarcopenia development. Nevertheless, the same recommendation does not have to be addressed to alcohol drinking. As in the study there was not found any relationship that supported the idea that alcohol drinking might make sarcopenia worse.

Implications for research

The implications for research would be summarized into three recommendations. First, there it would be more beneficial for sarcopenia diagnosing to exploit in trials the reference values according to the age, gender and ethnicity, which currently have been established by eminent authors and their summary has been recommended by EWGSOP; second, to use for ascertainment of exposure the valid tools e.g. "pack-years" or those proposed by the WHO. As an improvement of quality diagnostics method should bring better standard of studies and could contribute to better prevention and treatment of sarcopenia. Finally, it would be more useful to create study groups more similar according to the age. Those groups′ comparison would be much more meaningful.

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