Cardiovascular Risk Profile in Dupuytren's Disease: A Systematic Review and Meta-Analysis.

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Abstract

Background. Patients with Dupuytren's disease (DD) may have a higher cardiovascular (CV) risk because of association with diseases with a higher recognized CV risk, such as diabetes. However, DD is not always linked to these diseases; therefore, it seems relevant to assess the CV profile in DD.

Methods. We performed a systematic literature review up to April 2020. Differences between DD patients and controls were expressed as standardized mean differences using the inverse-variance method or as odds ratios (ORs) using the Mantel-Haenszel method.

Results. We obtained 51 references corresponding to 112,900 DD patients and 2,383,177 controls. We found a higher risk of death (OR=1.72 [95%CI:1.37-2.16]) and CV death (118/974 DD patients vs. 372/3948 controls; OR=1.33 [95%CI:1.07-1.66]) among DD patients compared to controls. DD patients were more often diabetic (OR=3.44 [95% CI:2.69-4.38]). In 17 studies of the general population, the incidence of diabetes was 17.5% among DD patients (11.7-24.2%). DD patients were older, and more often men or alcohol drinkers. The percentage of smokers and levels of blood pressure or total cholesterol were not different among DD patients and controls. No difference was found in triglycerides, but the risk of obesity was significantly lower in DD patients.

Conclusions. We found a higher CV risk in DD but not a higher prevalence of CV risk factors, except diabetes. This may be due to the predominance of men or greater number of alcohol drinkers or diabetics. Management of CV risk is important in patients with DD, including research on alcohol consumption or diabetes.

Background

Dupuytren's disease (DD) is characterized by contracture of the fourth and fifth fingers of the hand, and is common [1–3] but likely underestimated. Some patients are completely asymptomatic or hesitate to see their general practitioners because they consider DD to be shameful due to the supposed frequent association with alcohol consumption [4]. Alcohol intake is a risk factor for DD, but not the only one [5, 6]. Male patients are at higher risk of DD than women [6], although the sex predisposition may diminish with age [7]. The etiology of DD is still not well known [8]. Heredity has been proposed to be related to the pathogenesis of DD with an autosomal dominant pattern of inheritance [9, 10]. Diabetes is also recognized to highly increase the prevalence of DD, with a higher risk for type 1 diabetes mellitus [11]. Smoking is another factor that has been reported to increase the risk of DD [12]. Thus, patients with DD are more often men, smokers, diabetics, and alcohol consumers and, therefore, may have a higher incidence of cardiovascular (CV) morbidity or mortality. However, few studies have assessed this CV risk, and information is lacking on other CV risk factors (smoking, hypertension, dyslipidemia) in DD patients.

We performed a meta-analysis to increase the statistical power and accuracy of the available data regarding DD and CV risk. Our aims were to provide a more accurate assessment of the risk of developing CV events and the CV risk profile in patients with DD.

Methods

Literature search

We searched PubMed to find reports published since 9 April 2020. All observational or case-control studies monitoring death, CV events, such as myocardial infarction or stroke, or CV risk factors in DD patients were included. The following search terms were used: “(Dupuytren [tiab] AND (cardiovascular OR myocardial OR stroke OR atherosclerosis OR lipid OR diabetes OR glycemia OR glycaemia OR blood glucose))”. Our search included articles published in English or French. A manual search of references was also carried out. We collected data from the electronic abstract databases of the annual scientific meetings of the European League Against Rheumatism and American College of Rheumatology from 2009 to 2019 using the term "Dupuytren".

Trial selection

Two of us (SM and FD) selected potentially relevant articles after reading the title, keywords, abstract, and then full-text. Doubts about article selection were resolved by consensus with other authors. The inclusion criteria for the full-text were: study population comprised patients with DD; observational or case-control study; published in English or French before April 2020; data given on the number of smokers, diabetics, obese, or deceased, especially in the case of CV events, or mean and standard deviation (SD) for lipid profile parameters, blood pressure, and body mass index (BMI). The exclusion criteria were: commentary or discussion paper; case report or study including fewer than five patients; no data on CV risk or profile; did not include DD patients; full-text not available; or data not usable for statistical analysis (no SD or no interquartile range).

Data extraction

Two reviewers (SM and FD) extracted all data using a standardized data abstraction form. For all extracted data, a central value (mean or median) and variability (SD or interquartile range), or the number of patients with events of interest were obtained.

Quality of assessment

The two forms of the Newcastle-Ottawa Scale (NOS) were used, one for case-control studies and one for cohort studies, to check the quality of articles [13].

Statistical analysis

Continuous variables were expressed as weighted mean ± SD. The incidence of diabetes, smokers, or men among the DD and control populations were calculated by a meta-analysis of proportions (inverse-variance method). The Mantel-Haenszel procedure was used to determine the odds ratio (OR) for tobacco use, alcohol consumption, and other CV risk factors between DD patients and controls. This method provided a common OR estimate and 95% confidence interval (CI). For continuous variables age, blood

pressure, and total cholesterol, the differences between DD patients and controls were expressed by the standardized mean difference (SMD) using the inverse-variance method: moderate 0.2-0.8, large > 0.8. Statistical heterogeneity between results was assessed by examining forest plots, CIs, and I^2, which is the most common metric for measuring the magnitude of between-study heterogeneity and is easily interpretable. I^2 values range from 0% to 100% and are typically considered low when <25%, modest when 25-50%, and high when >50%. Random effects models were used if heterogeneity; otherwise we used a fixed effects model. Type-I error was fixed at α=0.05. Funnel plots of these meta-analyses were used to search for potential publication bias. To verify the strength of the results, further meta-analyses were conducted to exclude non-randomized studies and studies that were not evenly distributed around the base of the funnel. All of the items required in the PRISMA checklist were fulfilled in this study. This statistical analysis was conducted using Review Manager software (version 5.0) produced by the Cochrane Collaboration.

Results

Eligible studies

Figure 1 is a flow chart of publications identified by the literature search and the number finally retained. A total of 259 citations were obtained after research in the database. After reading the title, abstract, and full-text, we obtained 40 eligible studies, plus 1 by searching abstract databases and 10 by manual search, for a total of 112,900 patients with DD.

Study characteristics

Of the 51 publications, 1 was an abstract, 25 were case-control studies, 11 were cross-sectional studies, and 4 were longitudinal studies. Two studies assessed the risk of death and CV death in DD patients and controls. Forty-eight studies provided the CV characteristics (gender, tobacco and alcohol use, diabetes, hypertension, dyslipidemia, BMI) of DD patients. Thirty studies allowed comparisons of the CV risk profile between DD patients and controls (Supplementary file 1). The methodological quality of the included studies was good (Figure 2).

Characteristics of DD patients

The weighted mean age was 63.7 ± 11.3 years for 32,042 DD patients; 72.3% (n=37,976 [95% CI 62.5%-81.2%]) of DD patients were men, 40.4% (n=12,396 [95% CI 28.9%-52.4%]) were smokers, and 36.6% (n=13,361 [95% CI 18%-57.6%]) consumed alcohol. Nearly 40% of DD patients reported hypertension (39.5%, n=20,184 [95% CI 26.9%-52.7%]) and 19.3% (n=20,213 [95% CI 16.4%-22.4%]) had dyslipidemia. In all 33 studies providing data on diabetes and DD (n=48,602 patients), 44.5% (95% CI 37.5%-51.7%) of DD patients were diabetic. This percentage decreased to 17.5% (95% CI 11.7%-0.24%) in the 17 studies on the general population (n=47,375 patients) and increased to 78.2% (95% CI 60.7%-91.5%) in the 16 diabetics/control studies (n=1,227).

Risk of death

In three studies, 8,026 deaths were reported in DD patients (n=17,192) over a mean follow-up of 24 years (incidence 56.2% [95% CI 29.1%-81.4%], 2.3/100 person-years). Among controls, the incidence of death over 21 years (561 deaths in 1474 controls) was 50.2% [95% CI 3.5%-96.6%]. Two studies assessed the risk of death among DD patients compared to controls, and a meta-analysis of these two studies found a higher risk among DD patients (OR=1.72 [95% CI 1.37-2.16]). In the same way, DD patients had a 33% higher risk of death from CV disease (Figure 3) than controls.

Comparison of CV risk profile

Up to 23 case-control studies of diabetes distinguished DD patients (n=18,899) and controls (n=2,050,705). Figure 4 shows a comparison of characteristics between DD patients and controls. DD patients were older, more often men, and more likely alcohol drinkers. The percentage of smokers among DD patients and controls was not significant different. Similarly, DD patients were not more likely to have hypertension or high total cholesterol compared to controls. Triglyceride levels were not different among DD patients and controls. Surprisingly, DD patients were significantly less obese. Sensitivity analyses excluding studies outside the metafunnel demonstrated similar results (data not shown).

Discussion

In this meta-analysis, we found a 33% increased incidence of death, especially CV death, among patients with DD. This higher CV risk seemed to be due to a worse CV profile. DD patients were more often male, older, and with a higher consumption of alcohol. Diabetes was 3-fold more common in DD patients. However, other recognized CV risk factors were not increased in DD patients in this meta-analysis. We found no difference in the level of cholesterol and tobacco use. Therefore, as diabetes is a well-known risk factor for CV morbidity and mortality, we hypothesized that DD without diabetes may have the same CV risk as controls matched for age, sex, and alcohol intake. Unfortunately, no study has been designed to answer this question.

BMI was lower in DD patients compared to controls, as were the triglyceride levels. This finding is surprising because, with a higher consumption of alcohol and higher frequency of diabetes in DD patients, these patients would be expected to have a more frequent prevalence of metabolic syndrome, characterized by obesity and higher triglyceride levels [14]. These results could be explained by higher activity at work in patients with DD. Manual work was often reported in DD patients, which can be very physical with heavy or repetitive handwork [15, 16]. In three studies in this meta-analysis, DD patients performed manual work 2-fold more often than controls (data not shown).

We found no difference in smoking status between DD patients and controls in this meta-analysis, which is in contrast to other references that reported a higher risk in smokers [5, 17]. However, the proportion of smokers is important in our study, accounting for 76% of the DD population and 60% of controls. These percentages are important compared to the general population in Europe and France (26% and 32%,

respectively, in 2015) [18]. This suggests that the controls in our meta-analysis were not as healthy as those in the general population, which may explain why the percentage of smokers in the DD population was not significantly higher, though it is still very high.

DD is associated with diabetes and alcohol consumption, which play an important role in the physiopathology of DD. Management of CV risk in DD patients, such as with an assessment of 10-year CV risk using the Systematic Coronary Risk Estimation (SCORE) calculation or Atherosclerotic CV Disease (ASCVD) risk, seems important in the global evaluation of patients with DD, especially those with diabetes. The SCORE calculation using gender, total cholesterol total and HDL levels, systolic blood pressure, and tobacco use gives an estimation of global CV risk at 10 years and an indication for starting a healthy lifestyle and/or statins to reach the target LDL-cholesterol level [19–22]. Good control of diabetes with a low glycated hemoglobin level was reported to permit a decrease in CV risk [23, 24]. Moreno et al reported that glycated hemoglobin is an independent predictor of flow-mediated dilation, and a non-invasive marker of endothelial dysfunction in atheroma [25]. Similarly, discussing alcohol consumption is important in everyday management of DD (e.g., by general practitioners). Alcohol consumption and CV risk are still debated [26]. The dose of alcohol intake seems important. Chronic heavy drinking is well-known to have a detrimental impact on most major CV diseases, but the CV benefits of low-moderate alcohol consumption are still being questioned and may have been overestimated [27]. Less is best could be the good message for DD patients regarding alcohol consumption.

Our study has some limitations. First, the number of studies assessing CV events in DD patients was low. An association between diabetes and DD is well-known, and there are a lot of references in the medical literature, but the consequences of diabetes, such as occurrence of myocardial infarction or stroke, have not been studied sufficiently in the DD population. The two included studies represent nearly 1000 DD patients and 4000 controls. This is insufficient to draw strong conclusions on CV risk in DD, but is not negligible. Another limitation is related to publication bias. We cannot exclude that some investigations were not published because of insufficient interesting results or insufficient number of included patients. However, we searched relevant abstracts in European and American congresses and trial registries, such as PROSPERO (international prospective register of systematic reviews), and found no other references.

Conclusions

In this meta-analysis, we found that DD patients have a higher CV risk. Regarding the issue of CV risk evaluation, diabetes and alcohol use should be addressed in the management of DD patients during medical consultations.

List Of Abbreviations

ASCVD: Atherosclerotic Cardiovasculat Risk

BMI: Body mass index

CV: Cardiovascular

CI: Confidence interval

DD: Dupuytren's disease

NOS: Newcastle-Ottawa scale

OR: Odd ratio

SCORE: Systematic coronary risk estimation

SD: standard deviation

SMD: Standard mean difference

Declarations

Ethics approval and consent to participate: Not applicable for this meta-analysis

Consent for publication: Not applicable for this meta-analysis

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author (Dr Sylvain Mathieu, smathieu@chu-clermontferrand.fr) on reasonable request.

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Authors' contributions:

- Study conception and design. Mathieu, Dutheil, Pereira, Soubrier
- Acquisition of data. Mathieu, Dutheil
- Analysis and interpretation of data. Mathieu, Pereira, Dutheil, Soubrier

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Figures

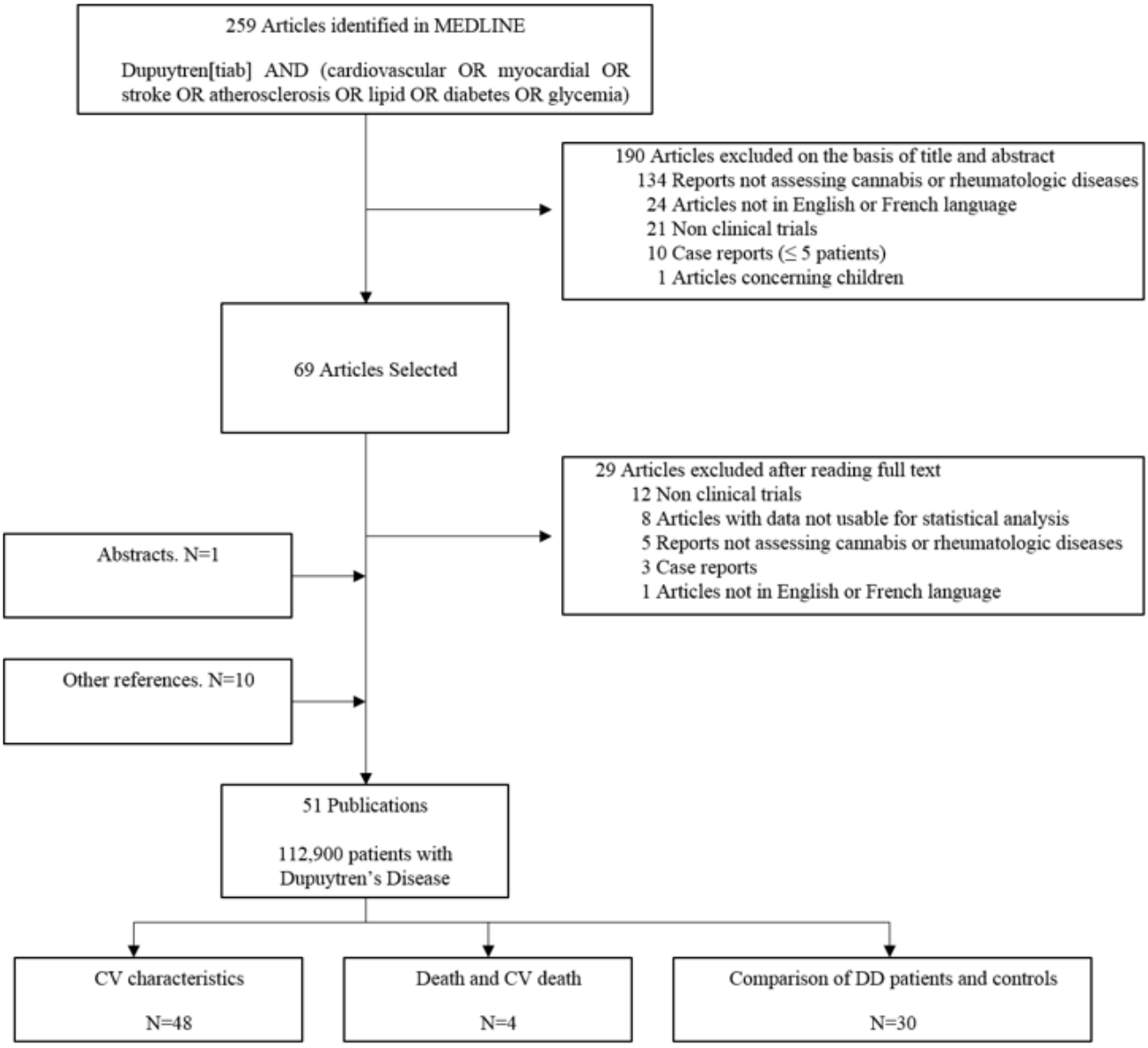

Figure 1

Flowchart of study selection

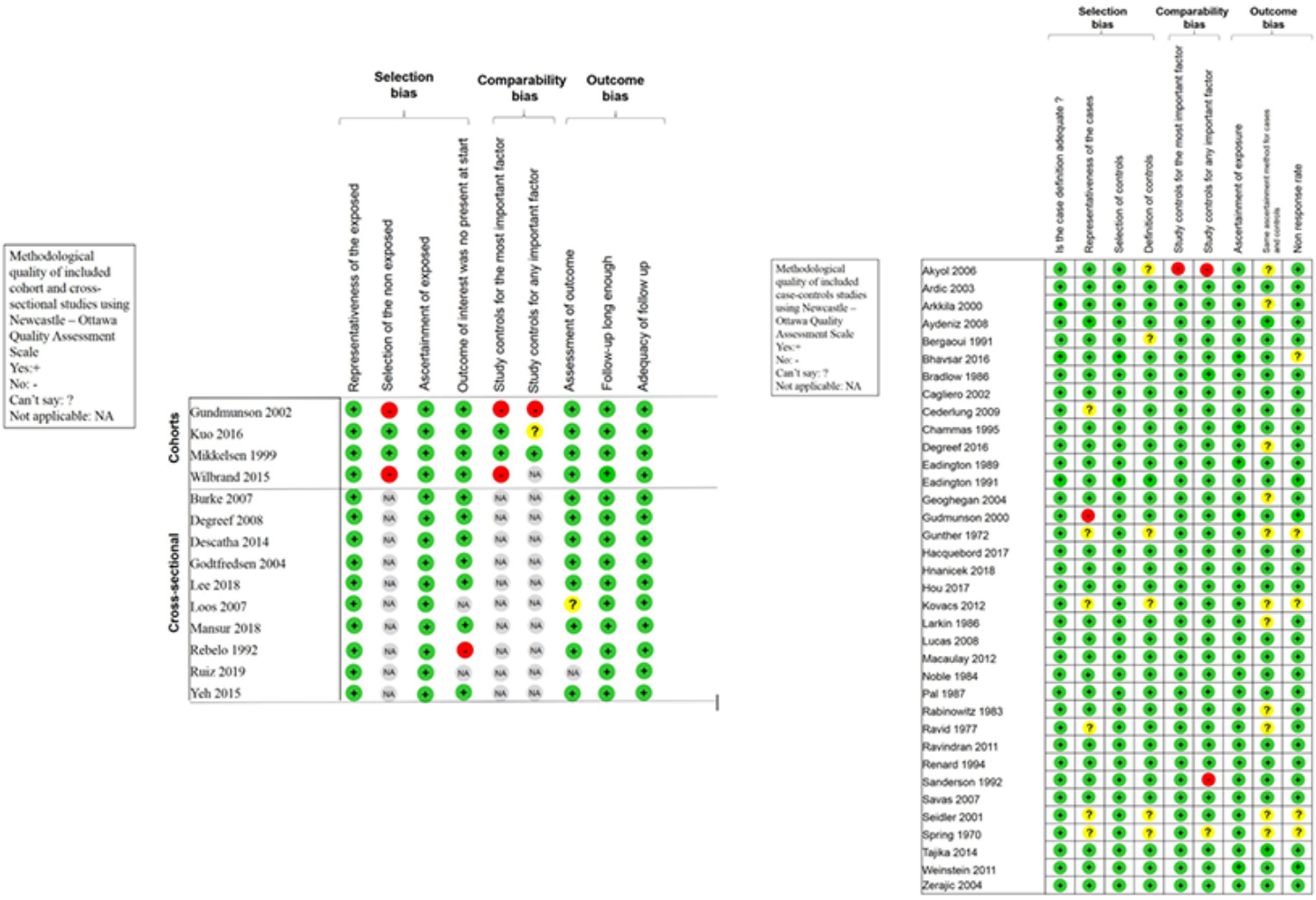

Figure 2

Methodological quality of included studies

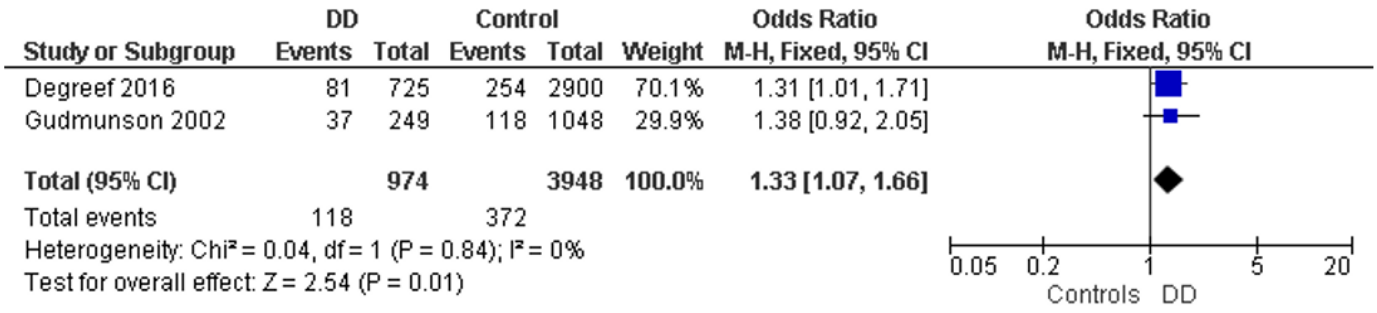

Figure 3

Forest plot of the risk of cardiovascular death between Dupuytren's disease (DD) patients and controls

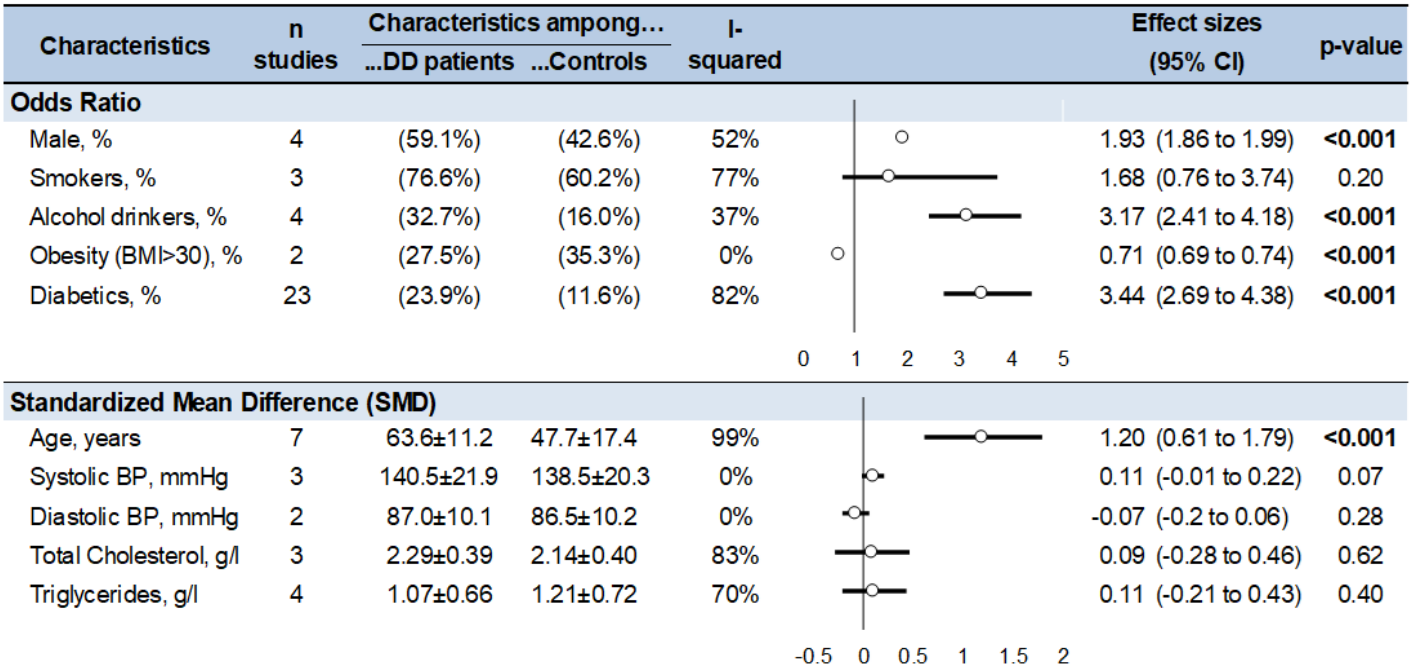

Figure 4

Comparison of characteristics between Dupuytren's disease (DD) patients and controls Age and systolic and diastolic blood pressure (BP) are given as weighted mean ± SD 8871 males/1,5019 DD patients, 867,859 males/2,037,044 controls;272 smokers/355 DD patients, 1031 smokers/1713 controls; 129 alcohol drinkers/394 DD patients, 430 alcohol drinkers/2689 controls; 4194 with obesity/15,224 DD patients, 719,334 with obesity/2,035,539 controls; 4518 diabetics/18,899 DD patients, 238,586 diabetics/2,050,705 controls.

Supplementary Files

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- Supplementaryfile1.docx