A systematic review and meta-analysis on the strength and consistency of the associations between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy

A Systematic Review and Meta-Analysis on the Strength and Consistency of the Associations between Dupuytren Disease and Diabetes Mellitus, Liver Disease, and Epilepsy

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Background: The role of diabetes mellitus, liver disease, and epilepsy as risk factors for Dupuytren disease remains unclear. In this systematic review and meta-analysis, the strength and consistency of these associations were examined.
Methods: The MEDLINE, EMBASE, and Web of Science databases were searched for articles reporting an association between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy published before September 26, 2016. The frequencies of Dupuytren disease and diabetes mellitus, liver disease, and epilepsy were extracted, as was information on potential confounders. Generalized linear mixed models were applied to estimate pooled odds ratios, adjusted for confounders. Heterogeneity between studies was quantified using an intraclass correlation coefficient and was accounted for by a random effect for study.
Results: One thousand two hundred sixty unique studies were identified, of which 32 were used in the meta-analyses. An association between Dupuytren disease and diabetes mellitus was observed (OR, 3.06; 95 percent CI, 2.69 to 3.48, adjusted for age), which was stronger for type 1 diabetes mellitus than for type 2 diabetes mellitus but was not statistically significant ($p = 0.24$). An association between Dupuytren disease and liver disease was observed (OR, 2.92; 95 percent CI, 2.08 to 4.12, adjusted for sex). Dupuytren disease and epilepsy were associated, yielding an OR of 2.80 (95 percent CI, 2.49 to 3.15). Heterogeneity between studies was moderate to low.
Conclusions: These findings demonstrate an association between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy. Prospective, longitudinal studies are needed to elucidate the pathways causing these associations. (*Plast. Reconstr. Surg.* 141: 367e, 2018.)

The precise cause of Dupuytren disease remains incompletely understood. Genetic factors are clearly involved in the pathogenesis of Dupuytren disease, as illustrated by family studies and by a genomewide association study.[1–3] In addition, environmental factors are believed to play a role in the development of the condition. Dupuytren disease has been observed in association with hand trauma, manual work, smoking, and excessive alcohol consumption.[4–7] Moreover, Dupuytren

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Received for publication February 28, 2017; accepted September 21, 2017.
Presented at the International Symposium on Dupuytren Disease, in Groningen, The Netherlands, May 22 through 23, 2015.

DOI: 10.1097/PRS.0000000000004120

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

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disease has often been linked to diseases such as diabetes mellitus, liver disease, and epilepsy.[4,8–12]

In particular, diabetes mellitus has frequently been studied in relation to Dupuytren disease, and diabetes mellitus is considered an important risk factor for the development of Dupuytren disease.[9,13,14] However, the studies reporting an association between Dupuytren disease and diabetes mellitus have conflicting results. In some studies, a strong association between the two conditions was observed,[15–17] but these results could not always be replicated in other studies.[18,19]

Liver disease has also frequently been associated with Dupuytren disease, although it is thought that excessive alcohol consumption might be responsible for this association. Therefore, it might be worthwhile to elucidate the role of alcohol consumption in this relation. The association between Dupuytren disease and epilepsy has frequently been the subject of study in older articles.[20–24] Again, some studies reported this association and others did not. This discrepancy may be caused by the fact that Dupuytren disease is thought to be associated with specific anticonvulsant drugs, mainly barbiturates, that are not often prescribed anymore. This might explain why some recent studies did not demonstrate an association between Dupuytren disease and epilepsy.[6,8]

In summary, the precise relationship between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy remains unclear. The discrepancy in study results may be caused by heterogeneity between study populations. Also, the lack of controlling for age or sex as confounding factors might lead to an incorrect estimation of the association. In addition, some small studies may individually be underpowered to show an association. Until now, no systematic review or meta-analysis has been conducted to estimate the strength of the association between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy. Therefore, the aim of the current study was to examine the strength and consistency of these associations in published studies reporting an association between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy, to end the ongoing debate about the role of diabetes mellitus, liver disease, and epilepsy as potential risk factors for Dupuytren disease.

PATIENTS AND METHODS

Literature Search and Article Assessment

A literature search was conducted on July 11, 2013, using the MEDLINE, EMBASE, and Web of Science databases, using the queries reported in Table 1. These queries were formulated in cooperation with an information specialist of our medical library. No restrictions on language or publication date were imposed. On September 16, 2016, the searches were updated.

Subsequently, two independent observers assessed the articles in three rounds, following the predefined inclusion and exclusion criteria as presented in Table 2. Although each article was assessed by only two observers, there were three observers in total [D.C.B., A.A.J.B. (see Acknowledgement), and S.M.]. Observer D.C.B. assessed all articles. Because of circumstances, the activities of observer A.A.J.B. were discontinued and carried on by observer S.M. In the first round, the titles and abstracts were assessed. If no abstract was available, the keywords and Medical Subject Headings terms were assessed. In case the keywords or Medical Subject Headings terms contained Dupuytren disease (or Dupuytren contracture, or fibromatosis) in combination with diabetes mellitus, liver disease, or epilepsy, the full text was screened. In all rounds, inconsistencies were discussed to come to consensus. If consensus could not be reached, a third observer (P.M.N.W.) was consulted. Articles were included if they provided sufficient data to calculate either the prevalence of Dupuytren disease in diabetes mellitus, liver disease, or epilepsy, or allowed the calculation of an odds ratio of these associations.

To correct for the confounding effect of age on the association between Dupuytren disease and diabetes mellitus, articles were included only if the age for both case and control groups was reported, or if the participants were matched on age. Sex is likely to be a confounder for the association between Dupuytren disease and liver disease; thus, we excluded the articles that did not report the sex in both case and control groups, or that did not match on sex. Because we could not identify potential confounders for the association between Dupuytren disease and epilepsy, there were no further exclusion criteria for this research question.

Data Extraction and Statistical Analyses

The primary outcome was the frequency of Dupuytren disease in the diabetes mellitus, liver disease, epilepsy, and control groups. The data were entered in a database by two observers independently. Articles that were published by the same authors having comparable titles were checked for data overlap. If the data overlap was larger than 50 percent, only the study reporting the most complete data was included

Table 1. Search Strategies Used for the Different Databases

Database	Search Query
MEDLINE	("Dupuytren Contracture"[Mesh] OR dupuytren*[TIAB]) AND (Epidemiol*[TIAB] OR "epidemiology" [Subheading] OR "etiology" [Subheading] OR associat*[TI] OR"Causality"[Mesh] OR "Epidemiologic Measurements"[Mesh])
EMBASE	dupuytren*:ab,ti AND ('epidemiology':ab,ti OR 'epidemiology'/exp OR 'epidemiological data'/exp OR 'etiology'/de OR 'disease association'/exp OR associat*:ti OR 'risk factor'/exp OR 'risk factor':ab,ti) NOT [medline]/lim AND [embase]/lim
Web of Science	TS=((dupuytren* AND (etiol* OR epidemiol*))) AND TI=((Dupuytren* OR fibromatos*)) AND TI=((etiol* OR epidemiol* OR associat*))

Table 2. Predefined Inclusion and Exclusion Criteria Used in the Different Rounds

Title and abstract
Inclusion criterion
Dupuytren disease as subject of research
Exclusion criteria
No original data/review
Not about association of DD and DM, liver disease, or epilepsy
Full-text analysis
Inclusion criterion
Articles in Dutch, German, French, or English language
Exclusion criteria
Not about association of DD and DM, liver disease, or epilepsy
No control group
No physical examination performed to diagnose DD
Case reports
Conference abstract
No original data
Data overlap (>50%)
Data extraction
Exclusion criteria
No data reported on age or sex, nor matched for age or sex
Incomplete data reported

DD, Dupuytren disease; DM, diabetes mellitus.

in the analyses. During the data extraction, the prevalence of Dupuytren disease was expressed in percentages of participants, and articles were excluded in case the prevalence was reported as percentages of hands.

Data were described by presenting the prevalence of Dupuytren disease, and ranges and forest plots are provided to show the odds ratios among studies. A generalized linear mixed model was used to estimate a pooled odds ratio using the procedure NLMIXED of SAS version 9.4 (SAS Institute, Inc., Cary, N.C.). (**See Document, Supplemental Digital Content 1,** in which detailed information on the statistical analyses is reported, ***http://links.lww.com/PRS/C637***.) The statistical analysis method used a generalized mixed model on the frequencies, with adjustment for potential confounders. Missing data on confounders were imputed.

Heterogeneity was calculated with the intraclass correlation coefficient. The larger the intraclass correlation coefficient value, the larger the heterogeneity. This value can be interpreted as a measure of consistency. (**See Document, Supplemental Digital Content 1,** in which detailed information on the statistical analyses is reported, ***http://links.lww.com/PRS/C637***.) In all statistical analyses, a significance level of 5 percent was used.

RESULTS

Results of the Literature Search

The initial search yielded 1309 articles, of which 1260 were unique (Fig. 1). After assessing the titles and abstracts, 166 articles were subjected to full-text analysis. Some articles reported data on two of the three diseases. These articles were included in all full-text analyses for the two diseases separately. This is the reason why the total number of articles included in the full-text analysis for diabetes mellitus, epilepsy, and liver disease combined, as presented in Figure 1, is larger than 166. In the full-text assessment round, the majority of articles were excluded because there was no control group included in the study. In three articles, a questionnaire was used to diagnose Dupuytren disease instead of a physical examination[7,25,26]; and in one article, the results were presented only for the number of hands, making it impossible to calculate an odds ratio on a participant level.[27] These articles were excluded from the analyses.

Of the 1260 unique articles that were obtained, 39 articles reported data on an association between Dupuytren disease and diabetes mellitus. Although many studies took the possible confounding effect of age into account by matching, in some studies this was lacking.[13,17,28–34] In a large number of articles, age was not reported for subgroups, nor were the participants matched on age.[4,12,15,18,19,35–42] These articles were therefore excluded, along with five articles that reported incomplete data.[27,43–46] A total of 21 articles were included in the meta-analysis on the association between Dupuytren disease and diabetes mellitus

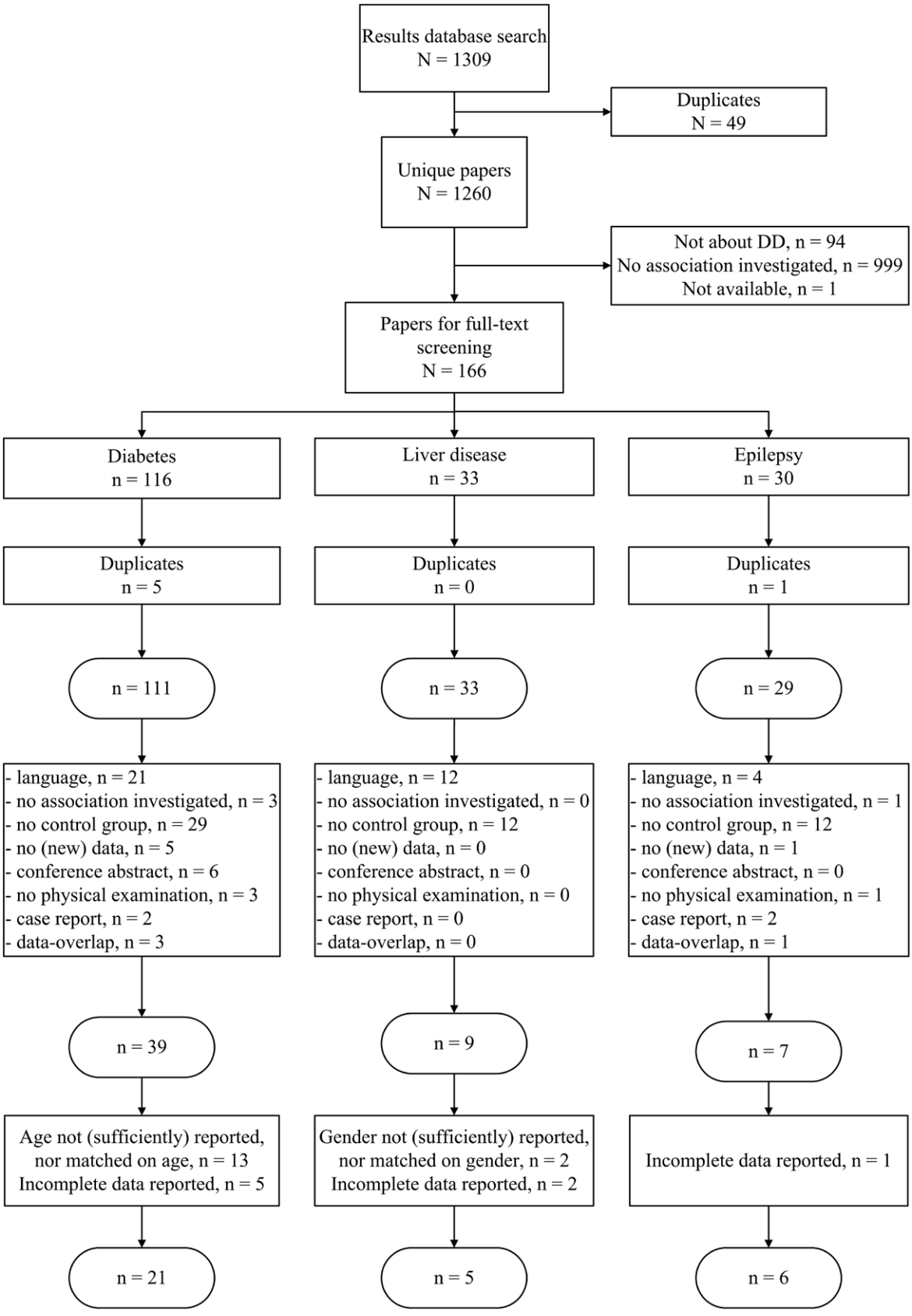

Fig. 1. Flowchart of the study selection process. *DD*, Dupuytren disease.

(Table 3). They all reported age of the diabetics and control group separately.

With respect to the association between Dupuytren disease and liver disease, nine articles reported data on an association (Table 4). In this association, a potential confounder is sex. The sex distribution was reported in almost all articles.[36,47] Two additional articles were excluded because they reported incomplete data.[39,40] Thus, five articles entered the meta-analysis (Table 4). One of the included articles reported that participants were matched on age and sex, but the sex distribution was not reported. The missing data on sex was imputed for this article.

Seven articles reported data on an association between Dupuytren disease and epilepsy. However, six articles were included in the meta-analysis (Table 5), because one article reported incomplete data.[39] One of the included articles provided data that were separated for the different types of anticonvulsant medication that the participants used.[8]

Dupuytren Disease and Diabetes Mellitus

The average prevalence of Dupuytren disease was 31 percent (range, 0.45 to 69 percent) in patients with diabetes mellitus (Table 3).[48,49] In controls, the mean average prevalence was 14 percent (range, 0.0 to 49 percent).[16,49] An association between Dupuytren disease and diabetes mellitus (irrespective of the type) was found, indicated by a pooled odds ratio of 3.06 (95 percent CI, 2.69 to 3.48). The heterogeneity between studies was moderate, indicated by an intraclass correlation coefficient of 0.56. This indicates that the consistency was also moderate, which corresponds with the findings with respect to the odds ratios (Fig. 2).

Almost half of the studies specified the type of diabetes mellitus, or reported data for the different types of diabetes mellitus separately.[13,16,28–30,50–53] For type 1 diabetes mellitus, the age-adjusted odds ratio was 3.90 (95 percent CI, 2.48 to 6.12), whereas for type 2 diabetes mellitus an odds ratio of 3.04 (95 percent CI, 2.18 to 4.23) was found. A difference between the odds ratios of type 1 and type 2 diabetes mellitus could not be demonstrated ($p = 0.24$). Heterogeneity was low, as indicated by an intraclass correlation coefficient of 0.05.

Dupuytren Disease and Liver Disease

The average prevalence of Dupuytren disease was 22.3 percent (range, 18.9 to 47.4 percent) in patients with liver disease (Table 4).[4,58] In controls, the average prevalence was 9.7 percent (range, 7.5 to 14.0 percent).[58,59] The sex-adjusted odds ratio of the association between Dupuytren disease and liver disease was 2.92 (95 percent CI, 2.08 to 4.12). Heterogeneity was low, as indicated by an intraclass correlation coefficient of 0.05, indicating that the association between Dupuytren disease and liver disease was consistent (Fig. 3). The majority of the studies included participants with liver cirrhosis,[4,57–59] and two articles made a distinction between alcoholic and nonalcoholic liver cirrhosis.[4,59] In one article, the type of liver disease was not reported.[60]

Dupuytren Disease and Epilepsy

The average prevalence of Dupuytren disease was 40.3 percent (range, 7.9 to 70.5 percent) in patients with epilepsy (Table 5).[49,61] In controls, the average prevalence was 29.2 percent (range, 6.0 to 49.2 percent).[49,61] There was an association between Dupuytren disease and epilepsy (OR, 2.80; 95 percent CI, 2.49 to 3.15). One of these studies provided an odds ratio that was smaller than 1, indicating that epileptic patients were less likely to have Dupuytren disease in this study (Fig. 4). The heterogeneity between studies was moderate, as indicated by an intraclass correlation coefficient of 0.55. Unfortunately, only one study reported frequencies for different medication types,[8] and thus further analyses on medication were not possible.

DISCUSSION

This meta-analysis showed that Dupuytren disease and diabetes mellitus are strongly associated, even after adjustment for age differences between groups. Furthermore, an association between Dupuytren disease and liver disease adjusted for sex, and between Dupuytren disease and epilepsy was found.

The finding that Dupuytren disease and diabetes mellitus are associated suggests that Dupuytren disease and diabetes mellitus may have common factors that contribute to their pathogenesis. The suspected disease mechanism relates to biochemical changes that occur as a result of diabetes mellitus. It is known that many complications of diabetes mellitus are caused by nonenzymatic glycation of proteins. In the literature, there is increasing evidence for the role of nonenzymatic glycation in fibrotic diseases that are associated with diabetes mellitus, such as cardiomyopathy.[62,63] The biochemical changes

Table 3. Characteristics of Studies Included in the Analysis on the Association between Dupuytren Disease and Diabetes Mellitus

Reference	Design*	Country	Study Size		Study Sample	No. with DD (%)		Adjusted for Age
			DM	Controls		DM	Controls	
Ardic et al. 2003[28]	Case-control	Turkey	78	37	Patients with DM2 and nondiabetic controls	17 (22)	1 (3)	NR
Aydeniz et al., 2008[50]	Case-control	Turkey	102	101	Patients with DM2 and nondiabetic controls	13 (13)	4 (4)	Yes, age-matched controls
Bergaoui et al., 1991[54]	Case-control	Tunisia	280	100	Patients with DM1 or DM2 and nondiabetic controls	79 (28)	9 (9)	Yes, age-matched controls
Cagliero et al., 2002[29]	Case-control	United States	200	100	Patients with DM1 or DM2 and nondiabetic controls	32 (16)	3 (3)	NR
Cederlund et al., 2009[51]	Case-control	Sweden	23	35	Patients with DM2 and nondiabetic controls	10 (43)	4 (11)	Yes, age-matched controls
Chammas et al., 1995[52]	Case-control	France	120	120	Patients with DM1 or DM2 and nondiabetic controls	39 (33)	10 (8)	Yes, age-matched controls
Chen et al., 2015[55]	Cohort	Taiwan	606,152	609,970	Patients with DM and nondiabetic controls	184 (0)	109 (0)	Yes, age-matched controls
Eadington et al., 1991[30]	Case-control	United Kingdom	200	170	Patients with DM2 and nondiabetic controls	47 (24)	31 (18)	NR
Geoghegan et al., 2004[8]†	Case-control	United Kingdom	118	2345	Patients with DM and nondiabetic controls	64 (54)	757 (32)	Yes, age-matched controls
Gunther and Miosga, 1972[56]	Case-control	Germany	1000	1000	Patients with DM and nondiabetic controls	96 (10)	27 (3)	Yes, age-matched controls
Kovacs et al., 2012[13]	Case-control	Romania	187	197	Patients with DM1 or DM2 and nondiabetic controls	54 (29)	29 (15)	NR
Macaulay et al., 2012[49]†	Case-control	United States	165	2647	Patients with DM and nondiabetic controls	114 (69)	1292 (49)	Yes, age-matched controls
Noble et al., 1984[14]	Case-control	United Kingdom	150	150	Patients with DM and nondiabetic controls	65 (43)	27 (18)	Yes, age-matched controls
Ouedraogo et al., 2009[48]	Case-control	Burkina Faso	220	440	Patients with DM1 or DM2, and nondiabetic controls	1 (0)	0 (0)	Yes, age-matched controls
Pal et al., 1987[31]	Case-control	United Kingdom	109	75	Patients with DM1 or DM2, and nondiabetic controls	21 (19)	7 (9)	NR
Ravid et al., 1977[17]	Case-control	Israel	110	1396	Patients with DM and nondiabetic controls	17 (15)	9 (1)	NR
Renard et al., 1994[53]	Case-control	France	120	120	Patients with DM1 or DM2, and nondiabetic controls	39 (33)	10 (8)	Yes, age-matched controls
Savas et al., 2007[16]	Case-control	Turkey	44	60	Patients with DM2 and nondiabetic controls	13 (30)	0 (0)	Yes, age-matched controls
Seidler et al., 2001[32]†	Case-control	Germany	54	582	Patients with DM and nondiabetic controls	32 (59)	261 (45)	NR
Spring et al., 1970[33]	Case-control	United States	400	500	Patients with DM and nondiabetic controls	83 (21)	27 (5)	NR
Zerajic and Finsen, 2004[34]	Cross-sectional	Bosnia and Herzegovina	292	915	Patients with DM and nondiabetic controls	123 (42)	181 (20)	NR

DD, Dupuytren disease; DM, diabetes mellitus; NR, not reported.
*Case-control studies were defined as studies including a group of patients suffering from DM, and a control group. Cross-sectional studies were defined as studies including one group, in which the presence of DM and DD was determined.
†In these case-control studies, the presence of DM was determined in a group of Dupuytren patients and in controls.

Table 4. Characteristics of Articles Included in the Meta-Analysis on the Association between Dupuytren Disease and Liver Disease

Study	Design*	Country	Study Size		Study Sample	No. with DD (%)		What Liver Disease	Adjusted for Sex
			Liver Disease	Controls		Liver Disease	Controls		
Attali et al., 1987[4]	Cross-sectional	France	212	174	Patients with alcoholic and nonalcoholic liver disease and nonalcoholic controls, or controls without chronic liver disease	40 (19)	22 (13)	Alcoholic cirrhosis, noncirrhotic alcoholic liver nonalcoholic chronic liver disease	NR
Bertrand et al., 1977[59]	Case-control	France	100	100	Patients with alcoholic and nonalcoholic liver disease and controls from general medical ward without liver disease and without alcohol intoxication as controls	43 (43)	14 (14)	Alcoholic cirrhosis, nonalcoholic cirrhosis	Sex-matched controls
Davidson et al., 1956[58]	Case-control	United States	57	53	Patients with liver disease and patients of wards of Boston City Hospital, without liver disease and rarely drinking alcohol as controls	27 (47)	4 (8)	Cirrhosis	NR
Noble et al., 1992[60]	Case-control	United Kingdom	82	100	Patients with liver disease and patients from fracture clinic as controls	18 (22)	8 (8)	NR	Sex-matched controls
Su and Patek, 1970[57]	Case-control	United States	133	142	Patients with liver disease and controls who were total abstainers or who drank only moderate amounts of alcohol	24 (18)	17 (12)	Cirrhosis	NR

DD, Dupuytren disease; NR, not reported.
*Case-control studies were defined as studies including a group of patients suffering from liver disease, and a control group. Cross-sectional studies were defined as studies including one group, in which the presence of liver disease and Dupuytren disease was determined.

Table 5. Characteristics of Articles Included in the Meta-Analysis on the Association between Dupuytren Disease and Epilepsy

Reference	Design*	Country	Study Size		Study Sample	No. with DD (%)		What Medication
			Epilepsy	Controls		Epilepsy	Controls	
Arafa et al., 1992[23]	Case-control	United Kingdom	715	555	Epileptic patients and nonepileptic patients from fracture clinic as controls	183 (26)	89 (16)	Phenytoin, phenobarbitone, primidone, carbamazepine
Geoghegan et al., 2004[8]†	Case-control	United Kingdom	22	2441	Epileptic patients and nonepileptic controls	10 (45)	811 (33)	Phenytoin, barbiturates, carbamazepine, valproate
Laplane and Carydakis, 1985[61]	Case-control	France	191	150	Epileptic patients and nonepileptic neurologic patients who never used barbiturates as controls	15 (8)	9 (6)	Barbiturates, primidone, phenytoin, valproate, carbamazepine, ethosuximide, clonazepam, diazepam
Lucas et al., 2008[12]	Cross-sectional	France	16	2194	Epileptic patients and nonepileptic controls	6 (38)	206 (9)	NR
Macaulay et al., 2012[49]†	Case-control	United States	112	2700	Epileptic patients and nonepileptic controls	79 (71)	1327 (49)	NR
Seidler et al., 2001[32]†	Case-control	Germany	6	622	Epileptic patients and nonepileptic controls	2 (33)	283 (46)	NR

DD, Dupuytren disease; NR, not reported.
*Case-control studies were defined as studies including a group of patients suffering from epilepsy, and a control group. Cross-sectional studies were defined as studies including one group, in which the presence of epilepsy and Dupuytren disease was determined.
†In these studies, the presence of epilepsy was determined in a group of Dupuytren patients and in controls.

that occur as a result of diabetes mellitus cause oxidative stress that produces advanced-glycated end-products.[63,64] Advanced-glycated end-products interact with advanced-glycated end-product receptors present on cell surfaces, which causes up-regulation of transforming growth factor (TGF)-β.[65] TGF-β plays a key role in the pathology of fibrotic diseases, and up-regulation has been associated with Dupuytren disease.[66,67] In addition, the up-regulation of TGF-β also causes synthesis of type III collagen, the type of collagen that is predominantly found in Dupuytren disease tissue.[68,69] Moreover, collagen tends to stiffen by cross-linking because of nonenzymatic glycation.[70] Furthermore, biochemical studies have shown that diabetes mellitus metabolites stimulate the development of myofibroblasts,[71] the most important cell in Dupuytren disease nodules. Thus, it has been shown that biochemical consequences of diabetes mellitus play an important role in fibrotic diseases. Therefore, it is likely that the same pathogenic pathways underlie the association between Dupuytren disease and diabetes mellitus. In addition, it is possible that the peripheral vascular changes that can occur as a consequence of diabetes mellitus aggravate the oxidative stress. This has previously been suggested as a trigger for Dupuytren disease.[72,73] There was no statistically significant difference between the odds ratio of diabetes mellitus type 1 and type 2.

We further demonstrated an association between Dupuytren disease and liver disease, although the type of liver disease could not be addressed in the meta-analysis, because the data were not reported separately. Unfortunately, the effect of alcohol consumption in this association could not be determined either, because only one included article reported the amount of alcohol consumed in each group.[4] However, we were able to correct the analysis for differences in sex distribution. Multiple studies have shown that men consume more alcohol than women,[74–77] although this difference has become less pronounced in the past decade.[78] Therefore, sex can be considered as a proxy variable for alcohol consumption. This way, one could argue that our analyses were corrected for the indirect effects of alcohol consumption. Interestingly, animal studies indicate that the formation of advanced-glycated end-products also plays a role in alcoholic liver disease.[79] Furthermore, both diabetes mellitus and alcohol consumption are responsible for alterations in glucose homeostasis.[80,81]

Our results showed that Dupuytren disease and epilepsy are associated, but the suspected

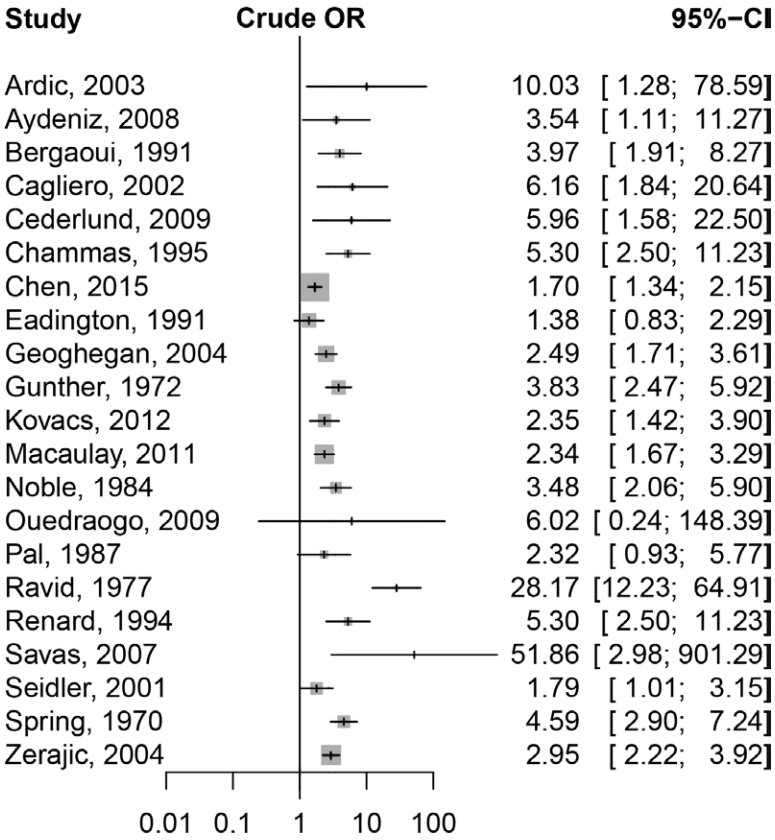

Fig. 2. Forest plot showing the association between Dupuytren disease and diabetes mellitus as calculated from the different articles. The size of the *square* indicates the weight of the study. The horizontal lines represent the 95 percent confidence interval. Note that this figure shows crude odds ratios.

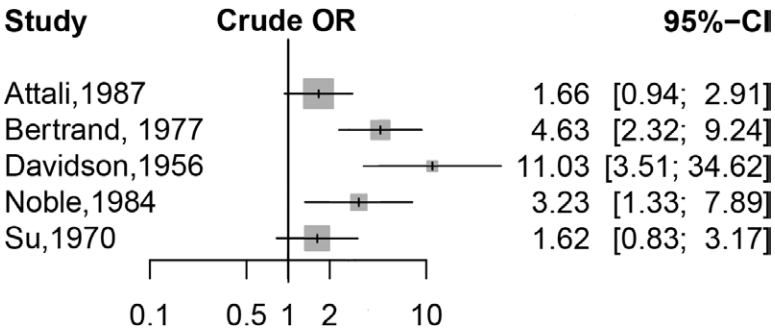

Fig. 3. Forest plot showing the association between Dupuytren disease and liver disease as calculated from the different articles. The size of the *square* indicates the weight of the study. Note that this figure shows crude odds ratios.

role of anticonvulsant medication could not be defined in this meta-analysis. However, one article that studied the association between Dupuytren disease and epilepsy reported data for each medication type separately.[8] In this article, an association between the two diseases was demonstrated, but no associations between specific anticonvulsants and Dupuytren disease were found. The authors argue that the association between the two diseases might be caused by ascertainment bias.

Publication bias is always a concern in meta-analyses. However, we did not look for funnel plot asymmetry, as the number of included articles was small. This was especially the case in the meta-analysis of Dupuytren disease and liver disease,

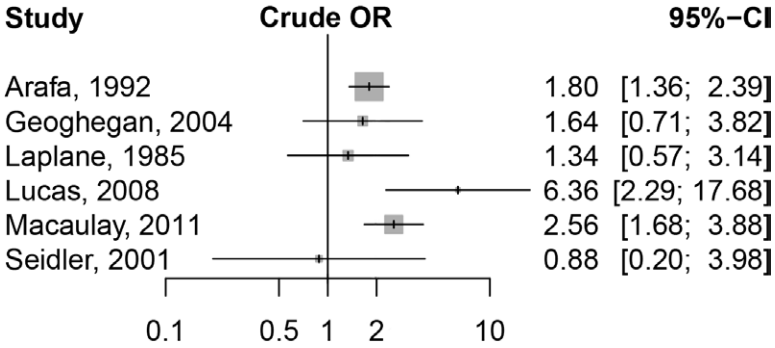

Fig. 4. Forest plot showing the association between Dupuytren disease and epilepsy as calculated from the different articles. The size of the *square* indicates the weight of the study.

and epilepsy. The statistical tests would lack power to identify asymmetry. Moreover, commonly used tests such as the Begg test or the Egger test cannot be used, because the outcome in this study is dichotomous. There are alternatives for examining funnel plot asymmetry in these cases[82] that are available in software packages such as R. However, these methods cannot manage meta-analyses in which covariates are included.

Although we planned to correct the association between Dupuytren disease and liver disease for the amount of alcohol consumed, this was not possible, because those data were not reported in the included studies. In such cases, it is advised to contact the authors for additional information. However, the included articles were published more than 20 years ago (1956 to 1992), making it difficult to contact the authors. Therefore, we want to emphasize that the results of our meta-analyses do not present information about causality. Furthermore, there were two articles in the association between Dupuytren disease and liver disease with a confidence interval overlapping 1.0. This indicates that the association was not significant, whereas the other articles demonstrated a significant association. However, the intraclass correlation coefficient indicated that heterogeneity was very low. Although this may seem contradictory, the point estimates of these studies were above an odds ratio of 1.0. The low intraclass correlation coefficient value ensures that this overlap is not caused by heterogeneity, but rather by a lack of sample size within studies, leading to a wide confidence interval. The same was seen in the association between Dupuytren disease and diabetes mellitus.

A weakness of this study is that the quality of the articles was not determined using a quality assessment tool. We had several reasons for this. First, there is no single quality assessment tool available for observational studies.[83,84] Second, and more importantly, there are multiple studies indicating that a quality score should not be used to weight, rank, or value the articles included in a meta-analysis.[85–88] Furthermore, the quality assessment score is often not related to effect size and heterogeneity.[89] The Cochrane Collaboration provides an alternative judgment system, evaluating risk of bias. However, this system is focused on randomized controlled trials and not on observational studies.

We noticed that the definition of Dupuytren disease varied widely across studies. For example, some authors did not report anything about the definition at all,[8,32,59] whereas others clearly stated the definition they used for Dupuytren disease.[23,28,58] (**See Table, Supplemental Digital Content 2,** in which details on diagnosis and definitions of Dupuytren disease and diabetes mellitus are reported, along with definitions of control groups and information on age as a potential confounder, ***http://links.lww.com/PRS/C638***. **See Table, Supplemental Digital Content 3,** in which details on diagnosis and definitions of Dupuytren disease are reported, along with definitions of control groups and information on sex as a potential confounder, ***http://links.lww.com/PRS/C639***. **See Table, Supplemental Digital Content 4,** in which details on diagnosis and definitions of Dupuytren disease are reported, along with definitions of control groups, ***http://links.lww.com/PRS/C640***.) Some only took alterations in the fourth or fifth digit into account.[33,54] Furthermore, the populations from which the control subjects were selected were diverse. In some studies, the controls were randomly selected from the general population,[32] whereas in other studies the controls were patients from a specific hospital department.[28] Although this increases the variability between studies, it would lead to an underestimation of the association strength rather than an overestimation.

Because of the correction for potential confounders, the results of these meta-analyses provide a more reliable estimation of the association between Dupuytren disease and diabetes mellitus, liver disease, and epilepsy. Future studies should elucidate the causal pathways that underlie these associations. Until then, clinicians and researchers studying Dupuytren disease should be aware of these associations and correct for them in their study design or analyses.

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ACKNOWLEDGMENT

The authors would like to thank Aletta A. J. Buurma, M.D., Ph.D., for help with screening the articles and collecting data.

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