Shared Genetics of Temporomandibular Disorder Pain and Neck Pain: Results of a Twin Study

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Aims: *(1)* To examine the heritability of TMD pain and of neck pain; and *(2)* to estimate the potential overlap in genetic and environmental factors influencing TMD pain and neck pain. **Methods:** Data from 2,238 adult female twins who completed a survey on TMD pain and neck pain were analyzed. The total variance of TMD pain and neck pain was decomposed into variance attributable to additive genetic effects and nonshared environmental effects. Bivariate structural equation modeling was applied to estimate trait-specific and genetic effects shared between traits. **Results:** The prevalence of TMD pain and neck pain was 8.6% and 46.8%, respectively, while 6.7% of the twins reported both TMD pain and neck pain. The phenotypic correlation between TMD pain and neck pain, based on a liability threshold model, was 0.43 (95% confidence interval [CI] 0.34 to 0.51). The heritability for TMD was 0.35 (0.17 to 0.51), and for neck pain was 0.33 (0.23 to 0.43). The genetic correlation between TMD pain and neck pain was 0.64 (0.35 to 1.00), and the environmental correlation was 0.32 (0.14 to 0.48). **Conclusion:** This study shows that variation in TMD pain and neck pain can in part be attributed to genes. The comorbidity between them is partly explained by genes that influence both traits and partly by the same environmental factors.
J Oral Facial Pain Headache 2018 (6 pages). doi: 10.11607/ofph.2016

Keywords: *heritability, neck pain, TMD pain, twin study*

Musculoskeletal pain conditions, such as temporomandibular disorder (TMD) pain and neck pain, often coexist.[1–4] Therefore, it seems plausible that such pain conditions share etiologic factors. Although the pathophysiology of these conditions is largely unknown, the biopsychosocial model is widely accepted to describe the factors that are involved in the development of pain. In support of this model, examples of risk factors found for TMD pain and neck pain are adverse habits (such as clenching or grinding teeth and work-related head posture), depression, and poor pain coping strategies.[5–8] Yet, many individuals with these characteristics do not suffer from musculoskeletal pain, while others without apparent abnormalities do report pain. Apparently, the complexity of the development and perpetuation of musculoskeletal pain complaints is only partly understood.

Evidence for the contribution of genetic factors to individual differences in pain for both experimental pain and clinical pain is growing.[9] Twin studies are a classic tool to study the separate contributions of heritability and environmental influences to a specific trait (eg, TMD pain or neck pain). In addition, they offer the unique possibility to examine potential overlap in the etiology of traits by evaluating the genetic and environmental influences that may explain the coexistence of these traits. In a recent review of twin studies on pain, the overlap in genetic contribution to the development of back pain and neck pain was estimated to be around 35%.[10] For TMD pain, only a few twin studies have been published.[11] The earlier twin studies found no evidence for heritability of TMD pain, but a recent twin study on shared genetics of TMD pain and migraine reported heritability of 27% for TMD pain.[12] In addition, a modest shared vulnerability for TMD pain and migraine headache in women was found, indicating that genes involved in the development of TMD pain are to some extent the same as those involved in migraine.

Given the limited number of studies on heritability of TMD pain and its high coexistence with neck pain, this study focuses on the genetic and environmental contribution to TMD pain and its possible shared etiology with neck pain. Therefore, the aims of this study were twofold: *(1)* to examine the heritability of TMD pain and of neck pain, and *(2)* to estimate the potential overlap in genetic and environmental factors influencing TMD pain and neck pain.

Materials and Methods

Data Collection

This study sample consisted of adult female twins registered with the Netherlands Twin Register (NTR: www.tweelingenregister.org).[13] As part of an ongoing longitudinal study, NTR participants receive invitations to participate in a survey every 2 to 3 years. This article is based on data from the ninth wave of questionnaire research in adult twins and their families. Details of this survey have been previously described.[4] Participants received an invitation letter with a personal login code for participation in a web-based survey that included questions regarding pain complaints. The letters were sent between January 2011 and February 2012. Participants were offered a hard copy of the survey on request. If they did not complete the survey within a couple of months after receiving the invitation, up to two reminders were sent. In July 2012, an email reminder was sent to those participants who had provided the NTR with their email address, and a letter was sent to twins whose co-twin had completed the survey to maximize the number of complete twin pairs. Finally, a selection of participants who had not completed the survey after the reminders were contacted by telephone, prioritizing participants who had previously supplied DNA samples or participants whose co-twin had completed the survey. Because of the low number of male twins with TMD pain in this sample (n = 34), the study focused on data from female twins. The study was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam (nr. 2010/130) and followed the ethical standards of the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study.

Measures

The pain sites assessed in the survey included, among others, TMD pain and neck pain. The TMD pain question was: "In the last year, did you experience pain in the face (eg, cheeks, temples, or jaw joints)?"; and the neck pain question was: "In the last year, did you experience neck ache?" For each pain question, the participant could rate the frequency of pain as no pain, occasionally, or a lot of the time. Because of the skewed distribution of the prevalence of the various pain types,[14] the outcomes were dichotomized as no pain and pain (representing both occasional and frequent pain). When a participant indicated having occasional or frequent pain at one of the measured body sites, a free-text box appeared to inquire about the cause of that pain. Afterwards, these free-text answers were screened to exclude apparent false positive answers to the pain questions. For the TMD pain question, which was preceded by a question on dental pain to prevent misclassification, reasons to recode the answer were: dental pain, neurologic pain, or pain due to a cerebrovascular incident (n = 149; 1.4% of the total sample). For neck pain, no recoding of the pain scores was indicated.

Sociodemographic variables included sex and age. Information on country of birth (the Netherlands vs any other country) and level of education (higher vocational college or university vs all other education) was available from previous surveys that were sent to the participants of the NTR.[13]

Statistical Analyses

In the classic twin design, the similarity between twins is used to estimate to what extent a trait is influenced by genetic effects, shared environmental effects, and nonshared (unique) environmental effects. Monozygotic (MZ, identical) twins share 100% of their genes, whereas dizygotic (DZ, fraternal) twins share on average 50%. Greater resemblance between MZ twins compared to DZ twins indicates additive genetic influences (A). MZ twin correlations smaller than twice the DZ twin correlations indicate that shared or common environmental influences (C) are also present (because MZ and DZ twins share these factors to the same extent). MZ correlations larger than twice the DZ correlations suggest the presence of not only additive, but also nonadditive genetic effects (or dominance) (D).[15] All environmental influences that are not shared among family members (ie, those environmental influences that make family members dissimilar) are represented by unique environment (E), which may also contain measurement error. So, based on the resemblance of MZ and DZ twins, the total variance of TMD pain and neck pain can be decomposed into variance attributable to A, to C or D, and to E (ie, an ADE, ACE, or AE model can be tested). Likewise, bivariate structural equation modeling can be applied to estimate trait-specific and genetic effects shared between traits; ie, TMD pain and neck pain. Since the pain variables were dichotomous, a liability threshold model was used that assumes that the observed categories reflect an underlying trait that is normally distributed, and tetrachoric correlations and heritability

 doi: 10.11607/ofph.2016

Table 1 Saturated Model–Fitting Results for Equating Thresholds for TMD Pain and Neck Pain

Model	−2LL	Compared with model	Δ−2LL (df)	*P*	AIC
0: Saturated	4,178.24	–	–	–	−4,573.76
1: Equal th twins TMD	4,183.41	0	5.17 (2)	.076	−4,572.59
2: Equal th twins neck pain	4,184.88	1	1.47 (2)	.480	−4,575.13
3: Equal th zyg TMD	4,187.02	2	2.14 (1)	.143	−4,574.98
4: Equal th zyg neck pain	4,188.18	3	1.16 (1)	.282	−4,575.83

−2LL = −2 log-likelihood; df = degrees of freedom; AIC = Akaike's Information Criterion; equal th twins = equal thresholds across twins; equal th zyg = equal thresholds across zygosity.

are estimated for this underlying trait of vulnerability to the disorders.

First, in a fully saturated model, all parameters were estimated without constraints; ie, the threshold (prevalences) and twin correlations. Next, reduced models were tested that assumed equal thresholds across twins (for TMD pain or neck pain prevalence, submodels 1 and 2, respectively) and equal thresholds across zygosity (submodels 3 and 4). The goodness of fit of each reduced model was compared to the previous model with a likelihood-ratio test. If the model fit did not significantly worsen compared to the previous model, the reduced model was used for the further analyses. Models were also evaluated using Akaike's Information Criterion (AIC), where a lower value indicates a superior fit.[16]

Three types of tetrachoric correlations were assessed: the phenotypic correlation (the association between TMD pain and neck pain within individuals), twin correlations (the within-pair similarity for a trait), and the cross-twin, cross-trait correlation (the correlation of TMD pain in the firstborn twin and neck pain in the secondborn twin, and vice versa).

Next, to estimate the relative contribution of genetic and environmental factors to the (co)variance of the traits, a bivariate genetic model was fitted to the data. Subsequently, parameters were removed from the model to evaluate their significance (with a significant likelihood-ratio test indicating the parameter cannot be dropped). In addition, the AIC of the submodels was evaluated. The final model was chosen based on parsimony and model fit (ie, the simplest model that explained the data well). Analyses were performed using R 2.14.2 and OpenMx version 1.3.2. *P* values below .05 were considered to indicate a significant deterioration of model fit.

Results

Study Population

Of the total number of 27,892 persons who were invited to participate, 11,948 persons responded (response rate = 43%). This included responses from twins (n = 5,637) and their family members (n = 6,311). Of the female twin respondents, 2,092 were MZ twins and 1,023 were DZ twins, and information on complete pairs was available for 789 MZ and 330 DZ pairs. Their mean (± SD) age was 38.0 ± 15.1 years, and their ages ranged from 20 to 90 years. The prevalence of TMD pain in this group was 8.6%, and the prevalence of neck pain was 46.8%; 6.7% of the twins reported both TMD pain and neck pain. In this female twin sample, 47.0% had a higher vocational college or university degree, and 98.2% were born in the Netherlands.

Genetic Modeling

Model-fitting results are presented in Table 1. Based on the results of the likelihood-ratio tests and the small differences in AIC, the model with equal thresholds for TMD pain and neck pain across first- and secondborn twins and across zygosity was preferred (model 4). Next, the phenotypic correlation between TMD pain and neck pain was estimated, as well as the twin correlations for both TMD pain and neck pain and the cross-twin, cross-trait correlations for MZ and DZ twins. The within-individual correlation was 0.43 (95% CI 0.34 to 0.51). Estimates of twin correlations and thresholds are shown in Table 2. The twin correlations for TMD pain showed the DZ correlation to be roughly half the MZ correlation, suggesting neither an effect of shared environmental factors (C) nor of a nonadditive genetic effect (D). Thus, a bivariate AE model was fitted to the data.

Bivariate genetic modeling results are presented in Table 3. The AE model (model 1) fitted the data well compared to the fully saturated model (Δ−2LL = 14.59; Δdf = 14; *P* = .41). The additive genetic correlation (*r*A) could not be omitted from the model (model 2), nor could the additive genetic variance specific to TMD (model 3). The A component specific to neck pain was borderline significant (model 7; *P* = .052). Based on the AIC, the AE model for both TMD and neck pain was preferred (model 1). Finally, a significant correlation was observed between the E components of both traits, which indicated that the nonshared environmental correlation could not be omitted from the model (model 5).

Table 2 Estimates of Female Twin Correlations for TMD Pain and Neck Pain and Cross-Twin, Cross-Trait Correlations

	TMD pain (95% CI)	Neck pain (95% CI)	Cross-twin, cross-trait (95% CI)
*r*MZ	0.35 (0.16 to 0.51)	0.36 (0.26 to 0.46)	0.22 (0.11 to 0.33)
*r*DZ	0.18 (–0.21 to 0.51)	.01 (–0.16 to 0.18)	0.08 (–0.11 to 0.26)
Threshold	1.36	0.08	–

*r*MZ = monozygotic twin correlation; *r*DZ = dizygotic twin correlation; 95% CI = 95% confidence interval.

Table 3 Genetic Model–Fitting Results

Model	–2LL	Compared with model	Δ–2LL(df)	*P*	AIC
1: AE both traits	**4,192.83**	**–**	**1.88 (1)**	**.170**	**–4,587.17**
2: AE, no *r*A	4,208.86	1	16.03 (1)	< .001	–4,573.14
3: E TMD, AE neck	4,217.42	1	24.58 (1)	< .001	–4,564.59
4: AE TMD, E neck	4,196.61	1	3.78 (1)	.052	–4,585.39
5: AE, no *r*E	4,205.35	1	12.52 (1)	< .001	–4,576.65

–2LL = –2 log-likelihood; df = degrees of freedom; AIC = Akaike's Information Criterion; A = additive genetic influences; E = nonshared environment; *r*A = additive-genetic correlation; *r*E = nonshared environmental correlation. Model 1 fitted the data best and was the preferred model.

Table 4 Parameter Estimates of Genetic Models for TMD and Neck Pain

AE model	A (95% CI)	E (95% CI)
TMD	0.35 (0.17 to 0.51)	0.65 (0.49 to 0.83)
Neck pain	0.33 (0.23 to 0.43)	0.67 (0.57 to 0.77)
Correlation	0.64 (0.35 to 1.00)	0.32 (0.14 to 0.48)
Explained covariance[a]	51%	49%

AE model = twin model without constraints on the variance components (equal thresholds across twin pairs and across zygosity are applied in all AE models); correlation = the additive genetic (A) or nonshared environmental (E) correlation. [a]Explained covariance between TMD pain and neck pain.

Table 4 presents estimates of variance components and genetic and environmental correlations for the final AE model. In this twin model, the heritabilities for TMD and neck pain were estimated at 0.35 and 0.33, respectively, and the proportions of variance explained by nonshared environmental influences were 0.65 and 0.67, respectively. The genetic correlation in the AE model was estimated at 0.64. Therefore, the contribution of additive genetic factors to the correlation between TMD and neck pain was (√0.35*0.64*√0.33) = 0.22. With a nonshared environmental correlation of 0.32, the contribution of nonshared environmental factors to the correlation of TMD and neck pain was (√0.65*0.32*√0.67) = 0.21. The phenotypic correlation between TMD and neck pain was 0.43 (see above). Thus, about 51% (0.22/0.43) of the correlation between TMD and neck pain was explained by shared genes, and about 49% (0.21/0.43) of the correlation between TMD and neck pain was explained by nonshared environmental factors.

Discussion

The phenotypic correlations showed that the presence of TMD pain in female twins was associated with the presence of neck pain, confirming earlier reports of the coexistence of the two types of musculoskeletal pain.[2–4] The heritabilities of TMD pain and neck pain were estimated at 35% and 33%, respectively. The bivariate analyses further showed that 51% of the covariance between TMD pain and neck pain was explained by genetic factors, and 49% was explained by nonshared environmental factors.

This study had several limitations. First, because of its large scale, the study was limited to the use of self-reported pain. For neck pain, the screening question was quite straightforward, but the screening for TMD pain was somewhat more complicated: It was described as pain in the face originating from pain in the cheeks, temples, or jaw joints. However, the most frequent cause for orofacial pain is dental pain.[17] To prevent misclassification, a question on dental pain was included preceding the TMD pain question in the questionnaire. In addition, the free-text boxes where participants could describe the presumed cause of their pain were checked. In case another type of pain was clearly mentioned, such as dental pain or facial pain caused by a cerebrovascular accident, the TMD pain question was corrected as being negative for TMD pain. The study's prevalences of TMD pain (8.6%) and neck pain (46.8%) were comparable with previous reports.[18,19]

Second, the options provided to the participants to describe their type of pain were "occasionally" and "a lot of the time." Even though the genetic response to chronic pain may be different to that of acute pain,

the time-framed description was chosen to prevent participants from having to interpret their pain in terms of chronic and acute; that is, because pain may come and go and this may confuse the participant on whether to label it as an acute pain on every new occasion or as a chronic pain, which recurs. Both types of pain were combined into the score "pain" for the analyses to cover both acute and chronic pain conditions. Third, the response rate was moderate (43%), which is comparable to previous studies in the adult NTR sample.[13] Still, the sample size was large (N = 11,948, including > 1,100 complete female twin pairs). In addition, previous research suggests little to no bias in the sample, as differences between responders and nonresponders are small with respect to lifestyle, personality, and mental health questionnaires in the NTR.[20] Fourth, the sample consisted mainly of participants born in the Netherlands (98.2%), and the participants were highly educated (47%). Even though the educational level is consistent with that of the Dutch population, the sample is biased toward Dutch natives (ie, higher educational level of the Dutch population = 51.1%, inhabitants born in the Netherlands = 89.0%[21]). Additionally, the study sample exclusively consisted of female participants, which limits the generalizability of the results toward male populations and people with other nationalities.

Only a few twin studies on TMD pain have been published before.[11] Sample size appears to be one of the most important factors affecting consistency of findings across twin studies.[10] Recently, in a large twin study, Plesh et al were the first to show a genetic contribution to TMD pain.[12] They reported a heritability of 27% for TMD pain in female twins, which is comparable to that found in the present study (35%). Some more twin studies are available for neck pain, with heritability estimates ranging up to 58%.[10] The largest study on neck pain included nearly 11,000 twin pairs and found heritability of 34% among females,[22] which is very similar to that found in the present study.

While the number of twin studies on musculoskeletal pain is limited, studies on genetic correlations between pain phenotypes are even more scarce. In a study on musculoskeletal pain at various anatomical sites (including neck pain, but not TMD pain), almost half of the genetic contribution found was estimated to be shared across the different pain sites.[23] In addition, Plesh et al reported on shared genetics between TMD pain and migraine headache.[12] The results of the present study extend these findings, as about half of the correlation between TMD pain and neck pain was explained by shared genes. The genetic correlation tells us to what extent two traits are influenced by the same set of genes: a perfect correlation would indicate the two traits are entirely influenced by the same genes, whereas a correlation of 0 would indicate an absence of genetic overlap. This type of information can provide a good basis for genetic association studies. When genetic variants are found for a specific phenotype (eg, neck pain) that are involved in the disease process, those genes are likely to be involved in the genetically correlated phenotype (eg, TMD pain) as well. In addition, knowledge on genetic correlations is also of great importance for selecting proper controls in genetic association studies. Since this study showed TMD pain and neck pain to be genetically correlated, a genetic association study comparing TMD pain patients to a population without TMD pain while ignoring the presence of neck pain in the control group will have a limited chance of success of finding genetic variants for TMD pain.

It is commonly accepted that multiple genes, each with a small individual effect, interact among themselves and with a variety of environmental factors to influence the individual vulnerability to developing chronic pain conditions.[9] In 2011, Maixner et al presented a model for the onset and persistence of TMD pain.[24] This model proposes that TMD pain is influenced by psychological distress and pain amplification, which in turn are subject to genetic regulation. The present study's outcomes on shared genetics for TMD pain and neck pain may help direct researchers involved in genetic association studies toward the detection of genes involved in various pain phenotypes.

Conclusions

This study has shown that TMD pain and neck pain are both partly heritable. Moreover, variance in these traits is partly explained by genes that influence both traits and partly by the same environmental factors.

Acknowledgments

L.L. was supported by a fellowship from the EMGO+ Institute for Health and Care Research. The authors declare that they have no conflicts of interest in relation to this manuscript. Birthe van Rossum and Britt de Visser are acknowledged for their participation in the data collection for this study. The authors also gratefully acknowledge grant NWO 480-15-001/674: Netherlands Twin Registry Repository: Researching the Interplay Between Genome and Environment, and they warmly thank all participants.

References

1. Macfarlane TV, Blinkhorn AS, Davies RM, Ryan P, Worthington HV, Macfarlane GJ. Orofacial pain: Just another chronic pain? Results from a population-based survey. Pain 2002;99: 453–458.

2. Plesh O, Adams SH, Gansky SA. Temporomandibular joint and muscle disorder-type pain and comorbid pains in a national US sample. J Orofac Pain 2011;25:190–198.
3. Visscher CM, Lobbezoo F, de Boer W, van der Zaag J, Naeije M. Prevalence of cervical spinal pain in craniomandibular pain patients. Eur J Oral Sci 2001;109:76–80.
4. Visscher CM, Ligthart L, Schuller AA, et al. Comorbid disorders and sociodemographic variables in temporomandibular pain in the general Dutch population. J Oral Facial Pain Headache 2015;29:51–59.
5. Bruls VE, Bastiaenen CH, de Bie RA. Prognostic factors of complaints of arm, neck, and/or shoulder: A systematic review of prospective cohort studies. Pain 2015;156:765–788.
6. Janwantanakul P, Pensri P, Jiamjarasrangsi W, Sinsongsook T. Associations between prevalence of self-reported musculoskeletal symptoms of the spine and biopsychosocial factors among office workers. J Occup Health 2009;51:114–122.
7. Manfredini D, Lobbezoo F. Relationship between bruxism and temporomandibular disorders: A systematic review of literature from 1998 to 2008. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;109:e26–e50.
8. Visscher CM, Lobbezoo F, de Boer W, van der Meulen M, Naeije M. Psychological distress in chronic craniomandibular and cervical spinal pain patients. Eur J Oral Sci 2001;109:165–171.
9. Fillingim RB, Wallace MR, Herbstman DM, Ribeiro-Dasilva M, Staud R. Genetic contributions to pain: A review of findings in humans. Oral Dis 2008;14:673–682.
10. Nielsen CS, Knudsen GP, Steingrímsdóttir ÓA. Twin studies of pain. Clin Genet 2012;82:331–340.
11. Visscher CM, Lobbezoo F. TMD pain is partly heritable. A systematic review of family studies and genetic association studies. J Oral Rehabil 2015;42:386–399.
12. Plesh O, Noonan C, Buchwald DS, Goldberg J, Afari N. Temporomandibular disorder-type pain and migraine headache in women: A preliminary twin study. J Orofac Pain 2012; 26:91–98.
13. Willemsen G, Vink JM, Abdellaoui A, et al. The Adult Netherlands Twin Register: Twenty-five years of survey and biological data collection. Twin Res Hum Genet 2013;16:271–281.
14. Ligthart L, Visscher CM, van Houtem et al. Comorbidity among multiple pain symptoms and anxious depression in a Dutch population sample. J Pain 2014;15:945–955.
15. Plomin R, DeFries JC, McClearn GE, McGuffun P. Behavioral Genetics. New York: Worth, 2008.
16. Akaike H. Factor analysis and AIC. Psychometrika 1987;52: 317–332.
17. De Leeuw R. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, ed 4. Chicago: Quintessence, 2008.
18. Carlsson GE. Epidemiology and treatment need for temporomandibular disorders. J Orofac Pain 1999;13:232–237.
19. Côté P, van der Velde G, Cassidy JD, et al. The burden and determinants of neck pain in workers: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine (Phila Pa 1976) 2008; 33(suppl):s60–s74.
20. Distel MA, Ligthart L, Willemsen G, Nyholt DR, Trull TJ, Boomsma DI. Personality, health and lifestyle in a questionnaire family study: A comparison between highly cooperative and less cooperative families. Twin Res Hum Genet 2007;10:348–353.
21. Central Bureau voor de Statistiek. Statistics Netherlands. http://statline.cbs.nl/Statweb/dome/?LA=en. Accessed 26 October 2017.
22. Fejer R, Hartvigsen J, Kyvik KO. Heritability of neck pain: A population-based study of 33,794 Danish twins. Rheumatology (Oxford) 2006;45:589–594.
23. Williams FM, Spector TD, MacGregor AJ. Pain reporting at different body sites is explained by a single underlying genetic factor. Rheumatology (Oxford) 2010;49:1753–1755.
24. Maixner W, Diatchenko L, Dubner R, et al. Orofacial Pain Prospective Evaluation and Risk Assessment Study—The OPPERA Study. J Pain 2011;12(suppl):T4–T11.