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3 **Maternal smoking during pregnancy is associated with offspring's musculoskeletal pain in**  
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5 **adolescence: Structural equation modeling**  
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**Abstract**

**Introduction:** Smoking and behavioral problems are related to musculoskeletal (MS) pain in adolescence. Maternal smoking during pregnancy (MSDP) is associated with offspring's behavioral problems but its relation to MS pain in adolescence is unknown. Our purpose was to investigate whether there is an association between MSDP, the number of pain sites in adolescence, and the factors that potentially mediate this relationship.

**Methods:** We evaluated the association of MSDP with offspring's MS pain at 16 years among participants of the Northern Finland Birth Cohort 1986 (n=6436, 3360 girls, 68% of all births) using Chi-square test and independent samples t-test. We used structural equation modeling (SEM) to assess the mediating factors stratified by gender.

**Results:** MSDP was frequent (22%) associating with paternal smoking ( $p<0.001$ ), externalization problems at 8 years ( $p=0.009$  boys,  $p=0.002$  girls), offspring's smoking at 16 years ( $p<0.001$ ), externalizing problems at 16 years ( $p<0.001$ ), family's social class ( $p<0.001$ ) and intactness of the family status ( $p<0.001$ ). The mean number of offspring's MS pain sites was higher among adolescents whose mothers had smoked during pregnancy than among those whose mothers were non-smokers ( $p=0.002$  boys,  $p=0.012$  girls). The association between MSDP and MS pain at 16 years was mediated by externalizing problems at 8 years ( $p<0.001$ ) and 16 years ( $p<0.001$ ).

**Conclusions:** MSDP increased the risk of offspring's MS pain in adolescence, and the association was mediated by offspring's externalizing problems during childhood and early adolescence.

### Implications

This study indicate that maternal smoking during pregnancy (MSDP) increases the risk of musculoskeletal pain in adolescence and the effect is mediated by externalizing problems. Our results add to the evidence on harmfulness of MSDP for offspring, and can be used as additional information in interventions aiming to influence MSDP.

For Peer Review

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## INTRODUCTION

Reporting of recurrent musculoskeletal (MS) pain already begins in pre-adolescence<sup>1</sup>, and is common in adolescence<sup>2</sup>. Multi-site pain is clinically relevant as it reduces quality of life more than single-site pain<sup>3-6</sup> and causes work disability<sup>7-9</sup>. Frequent MS pain in multiple body sites is related to behavioral and emotional problems, pessimistic beliefs regarding pain prognosis, poor mental health, and somatizing tendency<sup>7,10</sup>.

Previous studies have shown the relationship between smoking and MS pain as smokers consistently report more pain than non-smokers<sup>11-15</sup>. Our previous study of adolescents revealed that the association was stronger the higher the number of pain sites<sup>13</sup>. Several potential explanations have been suggested for this association, such as smoking-induced change of pain processing, modulation of neuroendocrine system via stress response, structural damage of peripheral tissue, and mood changes<sup>16</sup>.

Maternal smoking during pregnancy (MSDP) causes several health problems in the offspring, including impaired function of the endocrine, reproductive, respiratory, cardiovascular, and neurologic systems<sup>17</sup>. Children exposed to nicotine during pregnancy have poorer academic performance and significant emotional and behavioral problems during childhood and adolescence<sup>17-23</sup>. Nicotine exposure in utero has been associated with increased pain sensitivity among newborns<sup>24</sup> and primary headaches among schoolchildren<sup>25</sup>, but the effects of MSDP on offspring's MS pain in adolescence has not been investigated.

~~The association between maternal smoking during pregnancy (MSDP) and offspring's MS pain in adolescence has not been studied. However, MSDP is associated with emotional and behavioral problems among children and adolescents<sup>17-22</sup> and primary headache among schoolchildren<sup>23</sup>.~~

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3 Identifying early factors that affect the development of MS pain in adolescence is important to  
4 enable targeted interventions. Therefore, our purpose was to investigate whether there is an  
5 association between MSDP and the number of pain sites in adolescence, and whether psychological  
6 factors that potentially mediate this relationship. To answer this research question assess the  
7 potential mediating factors, we aimed to use the structural equation modeling (SEM) approach.  
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9 Our hypothesis was that MSDP is associated with MS pain in adolescence, as tobacco smoke  
10 constituents may affect, perhaps epigenetically, the organogenesis of the offspring. We also  
11 hypothesized that the association is at least partly explained by psychological problems in childhood.  
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## 24 METHODS

### 25 Study population

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28 The study population, the Northern Finland Birth Cohort 1986, consisted of children with an  
29 expected date of birth between 1<sup>st</sup> July 1985 and 30<sup>th</sup> June 1986 (n=9479) in the two northernmost  
30 provinces of Finland. Questionnaire-based data was collected during pregnancy, at the age of eight,  
31 and at the age of 15-16 (hereafter referred to as “16-year”). Questionnaires during pregnancy  
32 covered the biological, health, behavioral and socioeconomic characteristics of the mothers and  
33 families. The original sample collected at pregnancy represented 99% of all births for the time  
34 period in the area. At the age of 8, when 9297 children were alive and their addresses known,  
35 children's behavior, performance, and family conditions were elicited from parents (8370  
36 responded, 90%) and teachers (8525 responded, 92%). At the age of 16, when 9215 children were  
37 alive and their addresses known, adolescents were asked about their health, living habits, and social  
38 background (7182 responded, 78%). At this age, a postal inquiry was also sent to parents, including  
39 questions about family conditions (6866 responded, 75%). The present analyses include all cohort  
40 members who answered the MS pain questions at the age of 16 and whose mother reported their  
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3 smoking habits during pregnancy (n=6436, 68% of all births, 3360 girls and 3076 boys). The study  
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5 conformed to the principles of the Declaration of Helsinki. The participants took part voluntarily  
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7 and signed their informed consent, which was also obtained from their parents. The data was  
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9 handled on group level only and personal information was replaced by ID codes. The research  
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11 protocol was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District.  
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### 14 15 16 17 **Parental smoking during pregnancy**

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19 Maternal smoking during pregnancy was elicited during the first 24 gestational weeks and during  
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21 the last visit to the antenatal care unit or the first home visit after the delivery by asking: “Did you  
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23 smoke before pregnancy?”, “How long have you smoked? (years)”, “How many cigarettes?  
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25 (daily)”, and “Did you change your smoking habits during pregnancy?” If the mother had changed  
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27 her smoking habits, this was further clarified by eliciting type of change, month of pregnancy in  
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29 which the change occurred and number of cigarettes per day after the change. The variable was  
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31 formed and divided into two categories “never smoked or stopped at the very beginning of  
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33 pregnancy” and “smoked throughout the pregnancy or stopped smoking later during pregnancy”.  
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35 Paternal smoking was elicited from the mother by asking “Does your husband smoke?”. Response  
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37 options were yes or no.  
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### 45 46 47 **Emotional and behavioral problems at 8 years**

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49 At the age of 8 years, teachers and parents rated the children’s behavior during the previous year  
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51 using the Rutter scales<sup>26,27</sup>. The teachers' Rutter B2 scale included 26 items of which six are  
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53 considered to measure externalizing problems (e.g. ‘Fights every so often or quarrels often with  
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55 other children’ and ‘Bullies other children’) and four internalizing problems (e.g. ‘Is often worried’  
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57 and ‘Often seems low-spirited, unhappy, weepy or anguished’)<sup>27</sup>. The parents' Rutter A2 scale  
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3 originally had five externalizing and five internalizing items, but one externalizing and one  
4 internalizing item were removed for this study<sup>26</sup>. The parents' scale deviated from the original scale  
5 in that one item was dropped (externalizing scale: destroying belongings) and one was compiled  
6 from other questions (internalizing scale: fearful/nervous of school) because of the large number of  
7 questions and because they partly overlapped with some other questions included in the field study.  
8 The Rutter items were scored from 0 to 2 (0 = does not fit, 1 = fits partly, 2 = fits well)<sup>28</sup>. A single  
9 missing item in a subscale was imputed with the mean item score for the individual in the scale in  
10 question. If individuals had more than one missing item they were excluded from the data. The  
11 reliability and validity of the Finnish versions of the Rutter scales have shown to be appropriate<sup>29</sup>.

### 22 23 24 25 26 **Musculoskeletal pain at 16 years**

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29 At the age of 16 years, the inquiry included musculoskeletal pain questions: "Have you experienced  
30 pains or aches in any of the following parts of your body during the past six months?" (1) Head, (2)  
31 neck or occipital area, (3) shoulders, (4) low back, (5) elbows, (6) wrists and hands, (7) knees and  
32 (8) ankle-foot area. The response alternatives were: (a) no; (b) yes, but I have not consulted a  
33 physician, physiotherapist, nurse, or other health professional because of these pains; and (c) yes,  
34 and I have consulted a physician, physiotherapist, nurse, or other health professional because of  
35 these pains. Reporting pain and consultation for pain were combined. The pain sites were summed  
36 and used as a continuous variable, ranging from 0 to 8 pain sites, in the SEM analyses.

### 46 47 48 49 **Smoking at 16 years**

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52 Smoking status was elicited through the questions "Have you ever smoked in your life?", "Do you  
53 currently smoke?", and the frequency of smoking. Two categories were formed according to these  
54 questions: (1) not at all or occasionally, (2) 1–7 days per week.

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### Emotional and behavioral problems at 16 years

Emotional and behavioral problems at the age of 16 were assessed using the Youth Self-Report questionnaire<sup>30</sup> which is widely used and includes 105 syndrome/behavior items and eight syndrome subscales. Of the syndrome subscales, anxious/depressed symptoms, withdrawn/depressed symptoms and somatic complaints were further categorized as internalizing problems, and rule-breaking behavior and aggressive behavior as externalizing problems<sup>30,31</sup>. These two broader categories were used to describe adolescents' psychological status at 16 years and dichotomized to the normal, borderline or clinical range according to the recommended cut-off point of 82<sup>nd</sup> percentiles<sup>30</sup> for both gender separately. In the SEM analyses, externalizing and internalizing problems were used as continuous variables. Individuals with more than eight missing items (excluding open-ended and socially desirable items, altogether 15 items) were excluded from the analysis. Otherwise, the missing values were replaced by the mean value of other answered items of the particular subscale.

### Parental smoking when children were 16

Parental smoking was elicited when children were 16 years old: "Does the mother smoke now?" and "Does the father smoke now?" Both maternal and paternal smoking were categorized as non-smokers (including those who smoked occasionally) and smokers if they smoked 1–7 days per week.

### Family social class



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The social class of the parents was based on their education, which was elicited when the children were 16 years old. The family social class was classified as professional if at least one or other of child's parents had a polytechnic or university degree, or had passed the matriculation examination and completed post-secondary college. The rest of the families were classified as non-professional.

### **Change of family status**

Family status was considered from pregnancy to when the children were 16 years old. The variable was divided into two groups: "intact", if the family had stayed intact, and "non-intact", if the family was already non-intact during pregnancy (i.e. single parent) or had changed within the 16-year follow-up (e.g. divorce).

### **Statistical analyses**

All the analyses were stratified by gender. Different background factors and their associations with maternal smoking during pregnancy and offspring's number of MS pain sites were first studied using the Chi-square test and independent samples t-test. These results were used as the basis of the SEM analyses, as all background factors, which associated statistically significantly with the offspring's MS pain at 16 years were included in the SEM. As the focus was on MSDP, parental smoking during adolescence was also included in the SEM.

SEM is a statistical approach that includes a broad array of models, such as path analysis, confirmatory factor analysis and latent growth models. Statistically, SEM is an extension of general linear modeling procedures, such as regression analysis and analysis of variance. SEM is an appropriate method, as it is possible to simultaneously model series of structural equations<sup>32</sup>. Standardized regression coefficients are used to interpret the associations. Values of standardized

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3 regression coefficients indicate the expected difference on the criterion in standard deviation units,  
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5 controlling for all other predictors, so that these can be directly compared across predictors <sup>32</sup>.

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8 We used Comparative Fit Index and Root Mean Square Error of Approximation to check the  
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10 goodness of fit of the model. A Comparative Fit Index value of  $\geq 0.90$  and Root Mean Square Error  
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12 of Approximation value of  $\leq 0.05$  indicated a good fit. SPSS version 21 was used for the univariate  
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14 analyses and the SEM was performed using Mplus version 7 <sup>33</sup>.

## 20 21 RESULTS

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24 Maternal and paternal smoking was frequent during pregnancy (22% and 37%, respectively) with  
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26 no difference between the genders of the offspring (Table 1). At eight years, boys (12%) had more  
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28 externalizing problems than girls (8%;  $p < 0.001$ ), while at 16 years girls were more likely to smoke  
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30 (22% vs. 17%) and more likely to have both externalizing (26% vs. 16%) and internalizing  
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32 problems (20% vs. 11%;  $p < 0.001$  for all; Table 1). The mean of the number of pain sites was higher  
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34 among girls than boys (mean 3.1 vs 2.2,  $p < 0.001$ ).

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38 MSDP was associated with paternal smoking ( $p < 0.001$  for boys and girls), externalizing  
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40 problems at eight years ( $p = 0.009$  for boys,  $p = 0.002$  for girls), adolescents' smoking at 16 years  
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42 ( $p < 0.001$  for boys and girls), externalizing problems at 16 years ( $p < 0.001$  for boys and girls),  
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44 family's social class ( $p < 0.001$  for boys and girls) and intactness of family status ( $p < 0.001$  for boys  
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46 and girls), but not with internalizing problems at 8 or 16 years (Table 2).

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50 The mean of the number of pain sites was higher among girls than boys (mean 3.1 vs 2.2,  
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52  $p < 0.001$ ). There was a positive association between MSDP and the number of pain sites (mean 2.4  
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54 vs. 2.1,  $p = 0.002$  among boys; mean 3.2 vs. 3.1,  $p = 0.012$  among girls; Table 3). Among girls, the  
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56 number of pain sites was also associated with externalizing problems at 8 years (mean 3.5 vs. 3.1,  
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3  $p=0.002$ ), externalizing (~~mean 3.8 vs. 2.9,  $p<0.001$~~ ) and internalizing problems (~~mean 3.9 vs. 2.9,~~  
4  $p<0.001$ ) at 16 years, non-intact family status (~~mean 3.2 vs. 3.0,  $p=0.011$~~ ), maternal smoking at 16  
5 years (~~mean 3.3 vs. 3.1,  $p=0.005$~~ ), and offspring's smoking at 16 years (~~mean 3.6 vs. 3.0,  $p<0.001$~~ ).  
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7 Among boys, the number of pain sites was also associated with externalizing (~~mean 3.0 vs. 2.1,~~  
8  $p<0.001$ ) and internalizing problems (~~mean 3.2 vs. 2.1,  $p<0.001$~~ ) at 16 years, offspring's own  
9 smoking at 16 years (~~mean 2.5 vs. 2.1,  $p<0.001$~~ ), father's smoking at 16 years (~~mean 2.3 vs. 2.2,~~  
10  $p=0.040$ ) and non-intact family status (~~mean 2.5 vs. 2.1,  $p<0.001$~~ ), but not with externalizing  
11 problems at 8 years and mother's smoking at 16 years (Table 3).  
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21 The SEM showed a better fit of the model for boys (Comparative Fit Index = 0.990; Root Mean  
22 Square Error of Approximation=0.037, 90% CI = 0.029-0.045) but was also good for girls  
23 (Comparative Fit Index = 0.982; Root Mean Square Error of Approximation= 0.050, 90% CI =  
24 0.043-0.058; Figures 1 and 2). The relationship between MSDP and pain in adolescence was  
25 mediated by externalizing problems at both 8 years (girls:  $\beta=0.284$   $p<0.001$ ; boys:  $\beta=0.166$ ,  
26  $p<0.001$ ; Figures 1 and 2) and 16 years (girls:  $\beta=0.248$ ,  $p<0.001$ ; boys:  $\beta=0.251$ ,  $p<0.001$ ).  
27 Internalizing problems at 16 years also explained the number of pain sites (girls:  $\beta=0.194$ ,  $p<0.001$ ;  
28 boys:  $\beta=0.085$ ,  $p<0.001$ ) but not the relationship between MSDP and offspring's pain. ~~In addition~~  
29 ~~there was a strong association between externalizing and internalizing problems at 16 years (girls:~~  
30  ~~$\beta=0.442$ ,  $p<0.001$ ; boys:  $\beta=0.429$ ,  $p<0.001$ ).~~ The relationship between MSDP and pain in  
31 ~~adolescence was not mediated by social class or family intactness.~~  
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46 During pregnancy, paternal smoking was strongly associated with MSDP (girls:  $\beta=0.570$ ,  
47  $p<0.001$ ; boys:  $\beta=0.559$ ,  $p<0.001$ ; Figures 1 and 2) and MSDP predicted girls' smoking at 16  
48 ( $\beta=0.224$ ,  $p<0.001$ ). Parental smoking at 16 was strongly associated with offspring's smoking at 16  
49 years (girls:  $\beta=0.312$ ,  $p<0.001$ ; boys:  $\beta=0.367$ ,  $p<0.001$ ). Externalizing problems at 16 were also  
50 associated with offspring's own smoking at 16 (girls:  $\beta=0.482$ ,  $p<0.001$ ; boys:  $\beta=0.305$ ,  $p<0.001$ ).  
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3 Offspring's own smoking was associated with pain among girls ( $\beta=0.114$ ,  $p<0.01$ ) but not among  
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5 boys ( $\beta=-0.028$ ,  $p=0.361$ ).  
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## 10 11 **DISCUSSION**

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14 We showed an association between MSDP and offspring's MS pain at 16 years, evaluated by the  
15 number of pain sites. In the SEM analyses, the relationship was mediated by externalizing problems  
16 at the age of 8 and 16 in both genders. The mediating effect of the externalizing problems at 8 years  
17 seemed to be stronger among girls. In the SEM, we took into consideration paternal smoking,  
18 internalizing problems at 8 and 16 years, family's social class, intactness of family status, and  
19 offspring's smoking at 16 years in the link between MSDP and offspring's MS pain at 16.  
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21 However, internalizing problems at 16 years explained MS pain in both genders, while offspring's  
22 smoking at 16 years explained pain only among girls.  
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32 Previous studies have found an association between MSDP and offspring's behavioral problems  
33 such as hyperactivity disorder, hyperkinetic disorder and externalizing behavior in childhood and  
34 adolescence<sup>20,23,34,35</sup>. In a Dutch twin study, MSDP had an effect, although small, on externalizing  
35 problems at the age of three years, while no effect on internalizing behaviors was observed<sup>36</sup>. The  
36 amount of smoking and timing of smoking during pregnancy may be relevant as in the Finnish  
37 study consisting of the Northern Finland Birth Cohort 1986 sample<sup>18</sup>, a dose response effect  
38 between the amount of MSDP and hyperactivity was observed, while in another study the risk of  
39 externalizing behavior due to MSDP only increased in early but not in late pregnancy<sup>34</sup>. However,  
40 some negative associations between MSDP and offspring's externalizing behavior have been also  
41 reported<sup>37,38</sup>. The former study noticed no difference between siblings who differed in the exposure  
42 to prenatal nicotine<sup>37</sup>, while the latter conducted sibling-matched analysis in which the association  
43 was smaller than in the entire cohort<sup>38</sup>.  
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3 We are not aware of any studies on the relationship between MSDP and MS pain in adolescence.  
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5 However, it is reported that emotional and behavioral problems such as externalizing behavior in  
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7 adolescence may be associated with multiple MS pain in adolescence<sup>10,39</sup> and therefore a link  
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9 between MSDP and offspring's pain in adolescence is plausible. Smokers consistently report more  
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11 pain than non-smokers<sup>11-15,40,41</sup>. On the other hand, smoking has also been observed to have an  
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13 analgesic effect<sup>42,43</sup>.

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17 Nicotine and carbon monoxide are regarded as the most harmful components of tobacco smoke  
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19 for fetal brain development. The mechanisms include desensitization of nicotinic acetylcholine  
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21 receptors, fetal hypoxia and ischemia, and epigenetic changes such as altered methylation patterns  
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23 and microRNA expression<sup>44-46</sup>. MSDP is associated with impaired fetal head growth, decreased  
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25 volume of the cerebellum and corpus callosum, increased auditory brainstem responses, and lack of  
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27 coordination across brain regions during information and auditory processing<sup>45,47</sup>. It is hypothesized  
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29 that increased extra-synaptic dopamine in nucleus accumbens is crucial in nicotine-dependence<sup>48</sup>.  
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31 Interestingly, a greater functional connectivity of the nucleus accumbens with the prefrontal cortex  
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33 has predicted transition from acute to chronic back pain<sup>49</sup>. Therefore, the corticolimbic circuitry  
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35 between the medial prefrontal cortex and nucleus accumbens may be the common neural  
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37 mechanism between MSDP and offspring's pain in adolescence.  
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42 The strengths of our study include a large birth cohort, a high response rate and longitudinal  
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44 study design. The large longitudinal data set allowed us to study the association between MSDP and  
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46 adolescents' MS pain by taking into account several confounders in the SEM. Using the SEM, we  
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48 had the chance to observe latent and observed factors, and the relationships between these and MS  
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50 pain. The strength of the SEM is especially its flexibility, as it is possible to estimate complex  
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52 models, including both categorical and continuous, as well as observed and latent variables.  
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54 Limitations include the problem of omitted variables and potential limitations of models judged to  
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56 be well fitting<sup>50</sup>.  
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3 The Finnish version of the Youth Self-Report questionnaire has been standardized<sup>51</sup>, and initial  
4 support has been provided for the generalizability of the questionnaire's syndromes in various  
5 societies, including Finland<sup>52</sup>. The Youth Self-Report's psychometrics properties are considered  
6 good<sup>30</sup>. Although previously, the Rutter scales have been commonly used, our version of Rutter A2  
7 was slightly modified from the original version.  
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14 Our main limitation is that we relied on self-reported data, which may have led to inaccuracies  
15 due to, for instance, social desirability and recall difficulties. Unfortunately, our pain-related  
16 questions at 16 years did not include items on pain severity, such as pain-related limitations in daily  
17 activities, or pain duration and intensity. The lack of data on pain severity may have caused some  
18 overestimation of pain, and the minimal information regarding the nature of pain needs to be  
19 considered when interpreting and generalizing these results. However, our pain measure, number of  
20 pain sites at 16 years, is a relevant outcome as it is related to reduced quality of life and poorer work  
21 ability<sup>3-9,53</sup>.  
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33 We took into consideration family social class and family status in the analyses. Neither social  
34 class at 16 years nor intactness of the family status mediated the relationship between MSDP and  
35 pain in adolescence. We categorized social class on the basis of only the educational level of the  
36 family. In a Finnish study, both childhood and adult socio-economic position associated with  
37 radiating low back pain. However, the associations were complex, and varied according to socio-  
38 economic indicator and gender<sup>54</sup>. Therefore, we acknowledge that other ways of categorizing social  
39 class could be explored. Furthermore, we have no data on social deprivation, which is a limitation  
40 of the study.  
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52 The current study is, to the best of our knowledge, the first to evaluate the link between MSDP  
53 and offspring's MS pains in adolescence. Our results indicate that MSDP increases the risk of  
54 offspring's for MS pain symptoms in adolescence and the effect is mediated by externalizing  
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3 problems. Our results add to the large evidence on harmfulness of MSDP for offspring, and can be  
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5 used as additional information in interventions aiming to influence MSDP.  
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## 10 11 **FUNDING**

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14 This study received no external funding.  
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## 18 19 20 21 **COMPETING INTERESTS**

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24 There were no competing interests.  
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For Peer Review

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**Figure legends**

**Figure 1.** Structural equation modeling between maternal smoking during pregnancy and musculoskeletal pain at 16 years among girls. Rectangles present observed and ellipses latent variables, two-headed arrows indicate correlations and one-headed arrows regression paths. Statistically significant coefficients are in bold.

**Figure 2.** Structural equation modeling between maternal smoking during pregnancy and musculoskeletal pain at 16 years among boys. Rectangles present observed and ellipses latent variables, two-headed arrows indicate correlations and one-headed arrows regression paths. Statistically significant coefficients are in bold.

Table 1. Demographics of the study population at different time points according to gender.

Determinants	Girls (n=3360)	Boys (n=3076)	P value <sup>a</sup>
	n (%)	n (%)	
During pregnancy			
Maternal smoking			0.857
No	2606 (77.6)	2392 (77.8)	
Yes	754 (22.4)	684 (22.2)	
Paternal smoking			0.828
No	1896 (62.9)	1771 (63.2)	
Yes	1118 (37.1)	1032 (36.8)	
At eight years			
Externalizing problems			<0.001
Normal	2780 (92.2)	2413 (88.2)	
Problem	234 (7.8)	322 (11.8)	
Internalizing problems			0.480
Normal	2665 (88.3)	2433 (89.0)	
Problem	352 (11.7)	302 (11.0)	
At sixteen years			
Adolescent's smoking			<0.001
No	2601 (78.2)	2474 (82.6)	
Yes	726 (21.8)	520 (17.4)	
Mother's smoking			0.708
No	2347 (80.8)	2197 (81.2)	
Yes	558 (19.2)	508 (18.8)	
Father's smoking			0.758
No	2015 (72.8)	1874 (73.2)	
Yes	753 (27.2)	687 (26.8)	
Externalizing problems			<0.001
Normal	2485 (74.3)	2553 (84.4)	
Problem	860 (25.7)	472 (15.6)	
Internalizing problems			<0.001
Normal	2665 (80.5)	2668 (88.7)	
Problem	647 (19.5)	340 (11.3)	
Social class of family			0.482
Non-professional	2005 (67.1)	1884 (68.0)	
Professional	983 (32.9)	887 (32.0)	
Change of family status			0.048
Intact	2062 (75.3)	1981 (77.6)	
Non-intact	676 (24.7)	571 (22.4)	

<sup>a</sup>Fisher's exact test was used for analyzing gender difference.

Table 2. The prevalence of maternal smoking during pregnancy according to determinants at different time points.

	Girls		Boys	
	n (%)	<i>P</i> value <sup>a</sup>	n (%)	<i>P</i> value <sup>a</sup>
During pregnancy				
Paternal smoking		<0.001		<0.001
No	222 (11.7)		220 (12.4)	
Yes	456 (40.8)		418 (40.5)	
At eight years				
Externalizing problems		0.002		0.009
Normal	603 (21.7)		501 (20.8)	
Problem	72 (30.8)		88 (27.3)	
Internalizing problems		0.946		0.236
Normal	599 (22.5)		516 (21.2)	
Problem	80 (22.7)		73 (24.2)	
At sixteen years				
Smoking		<0.001		<0.001
No	483 (18.6)		478 (19.3)	
Yes	262 (36.1)		186 (35.8)	
Mother's smoking		<0.001		<0.001
No	223 (9.5)		219 (10.0)	
Yes	399 (71.5)		364 (71.7)	
Father's smoking		<0.001		<0.001
No	285 (14.1)		262 (14.0)	
Yes	294 (39.0)		260 (37.8)	
Externalizing problems		<0.001		<0.001
Normal	491 (19.8)		528 (20.7)	
Problem	258 (30.0)		148 (31.4)	
Internalizing problems		0.052		0.052
Normal	579 (21.7)		579 (21.7)	
Problem	164 (25.3)		90 (26.5)	
Social class of family		<0.001		<0.001
Non-professional	507 (25.3)		475 (25.2)	
Professional	135 (13.7)		125 (14.1)	
Change of family status		<0.001		<0.001
Intact	334 (16.2)		312 (15.7)	
Non-intact	243 (35.9)		225 (39.4)	

<sup>a</sup>Fisher's exact test was used for the association between maternal smoking and each determinant.



Table 3. The mean number (SD) of musculoskeletal pains at 16 years according to determinants at different time points.

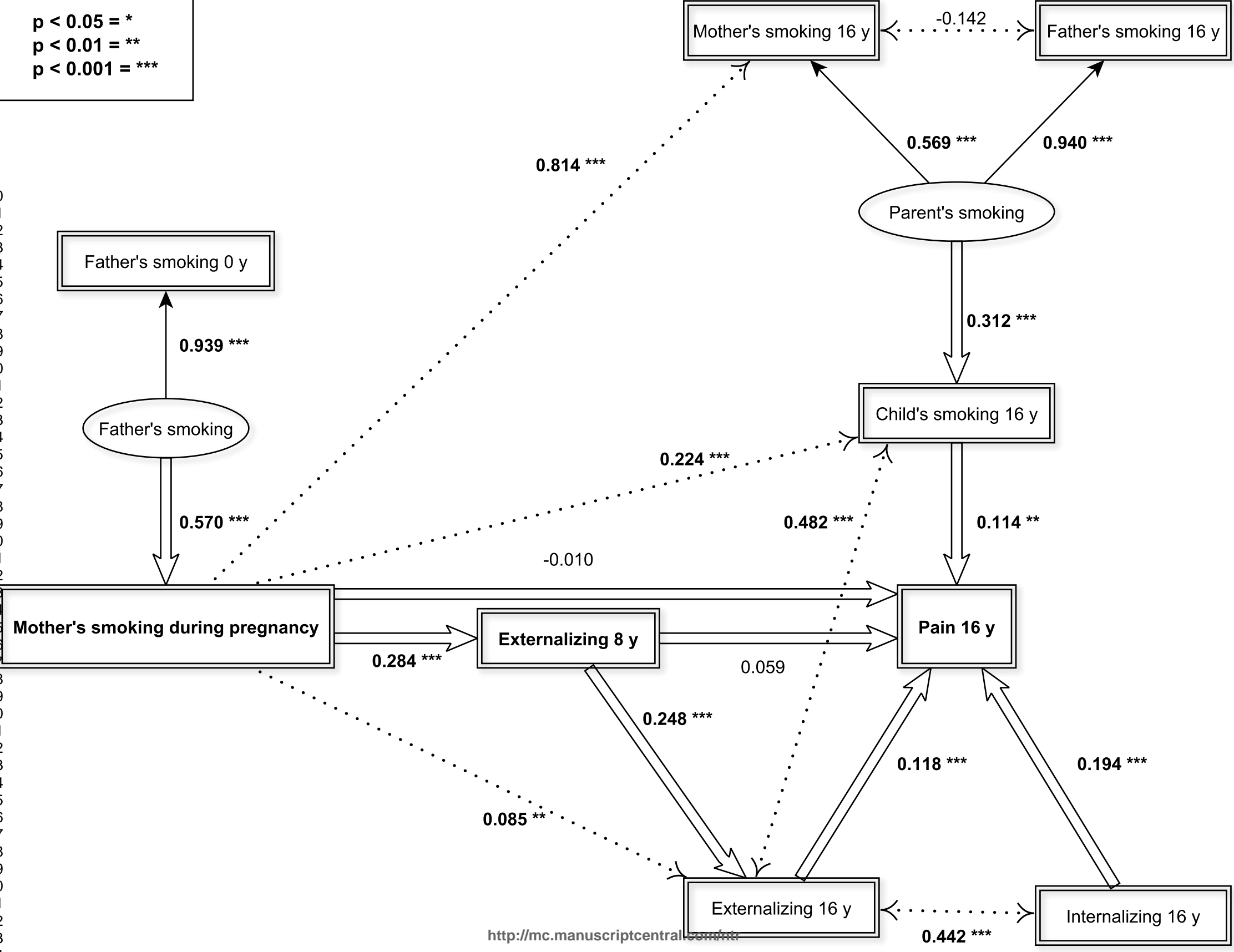
	Girls (n=3360)		Boys (n=3076)	
	Mean NPS (standard deviation)	<i>P</i> value <sup>a</sup>	Mean NPS (standard deviation)	<i>P</i> value <sup>a</sup>
All	3.09 (1.80)		2.19 (1.89)	
During pregnancy				
Maternal smoking		0.012		0.002
No	3.05 (1.79)		2.14 (1.87)	
Yes	3.23 (1.83)		2.39 (1.93)	
Paternal smoking		0.685		0.404
No	3.07 (1.81)		2.16 (1.88)	
Yes	3.10 (1.80)		2.22 (1.90)	
At eight years				
Externalizing problems		0.002		0.201
Normal	3.08 (1.79)		2.17 (1.88)	
Problem	3.46 (1.92)		2.32 (1.88)	
Internalizing problems		0.415		0.904
Normal	3.09 (1.79)		2.19 (1.88)	
Problem	3.17 (1.85)		2.21 (1.89)	
At sixteen years				
Smoking		<0.001		<0.001
No	2.97 (1.79)		2.14 (1.86)	
Yes	3.55 (1.75)		2.49 (1.98)	
Mother's smoking		0.005		0.319
No	3.05 (1.77)		2.18 (1.87)	
Yes	3.28 (1.80)		2.27 (1.90)	
Father's smoking		0.656		0.040
No	3.06 (1.77)		2.15 (1.88)	
Yes	3.10 (1.77)		2.32 (1.87)	
Externalizing problems		<0.001		<0.001
Normal	2.85 (1.76)		2.06 (1.80)	
Problem	3.77 (1.75)		2.97 (2.08)	
Internalizing problems		<0.001		<0.001
Normal	2.88 (1.75)		2.07 (1.80)	
Problem	3.94 (1.75)		3.19 (2.13)	
Social class of family		0.928		0.323
Non-professional	3.09 (1.81)		2.22 (1.89)	
Professional	3.09 (1.75)		2.15 (1.86)	
Change of family status		0.011		<0.001
Intact	3.03 (1.77)		2.12 (1.84)	
Non-intact	3.24 (1.81)		2.48 (1.94)	

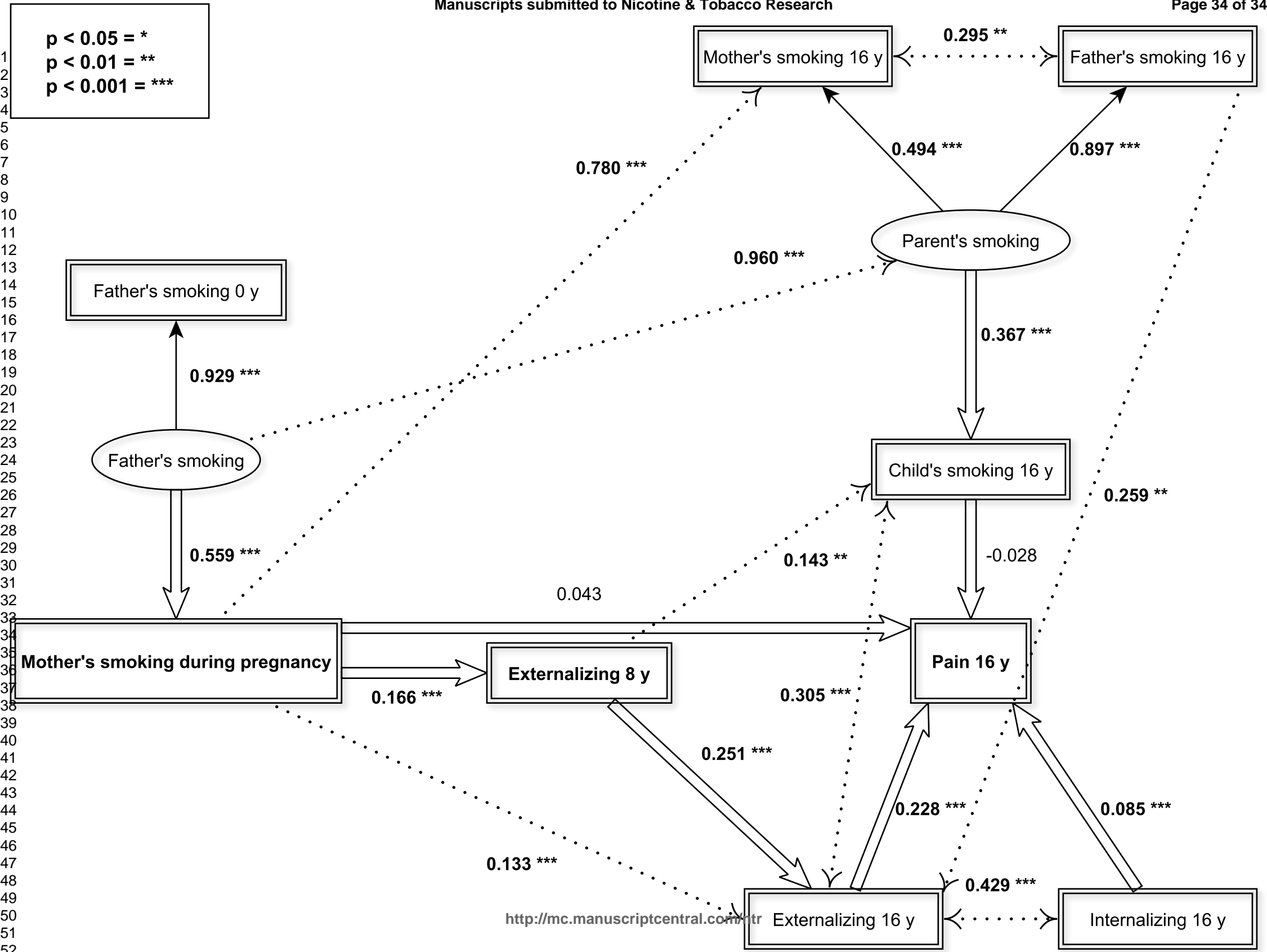
NPS = number of pain sites

<sup>a</sup>Independent samples t-test was used for the association between musculoskeletal pain and each determinant.

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