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Genetics of the association between intelligence and nicotine dependence: a study of male Swedish twins

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ABSTRACT

Aims Previous studies have found inverse associations between intelligence quotient (IQ) and cigarette smoking, but the causal pathways linking IQ with smoking status and nicotine dependence (ND) are not well understood. The aim of this study was to explore the associations between IQ and ND using a genetically informative twin design to detect whether any association is because of shared genetic or environmental factors. **Design** A population-based twin cohort with IQ measured in adolescence and ND later in life, analysed by classical twin modeling based on linear structural equations. **Setting** Swedish national registry data. **Participants** A total of 5040 male twins born 1951–84. **Measurements** IQ was measured at military conscription at a mean age of 18 years. ND was self-reported at the ages of 22–57 years using the Fagerström Test for ND scale (FTND). Both cigarette smoking and Swedish snus use were analysed. **Findings** Both IQ and ND showed moderate heritability (0.58 and 0.39, respectively). The heritability of ND was similar for cigarette smoking and snus use. The phenotypic correlation between IQ and ND was weak: –0.11 (–0.16, –0.06) for total ND. Bivariate analysis revealed that this correlation was mainly because of genetic factors, but still the genetic correlation between IQ and ND from cigarette smoking was only –0.24. **Conclusions** Nicotine dependence, as measured by the Fagerström Test for Nicotine Dependence, shows moderate heritability in both smokers and snus users but is only weakly associated with intelligence quotient; common genetic factors underlying nicotine dependence and intelligence quotient probably account for little of the observed association between smoking and intelligence quotient.

Keywords Health behaviour, intelligence, nicotine dependence.

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INTRODUCTION

Smoking has been suggested as a possible mediator of the established association between intelligence quotient (IQ) and cardiovascular disease (CVD) mortality [1–3]. Several studies have explored the association between IQ and smoking status and found inverse associations, i.e. the higher the IQ, the lower the risk of being a smoker [4–9]. It is often hypothesized that this association is either explained by socio-economic factors or arises because individuals with low IQ have difficulties understanding health messages and acting in accordance with them. However, there is little research exploring the underlying mechanism of the IQ–smoking association. In a previous twin study, we found that genetic and/or environmental factors largely explained the association between IQ and smoking [10]. In that study, the effect of IQ on persistence of and giving up smoking was not studied. However, the comparison between current and past smokers did suggest that IQ was related to giving up smoking [10]. Nicotine dependence (ND) is what keeps most smokers from quitting, and studying the association between IQ and ND, as well as the overlapping or distinct genetic and environmental factors behind the two traits, could contribute to an increased knowledge about a possible association between IQ and smoking persistence.

Associations between IQ and ND have been explored in few previous studies. Fergusson *et al.* studied the

associations between IQ at the age of 8–9 years and several outcomes, such as crime, substance use disorders, smoking and ND later in life [11]. Low IQ was found to be associated with the risk of ND at the age of 25 years. Azizian *et al*. examined performance on two types of cognitive tests among smokers and non-smokers and also measured severity of ND in smokers [12]. They found that smokers with a high level of ND performed worse on the tests than non-smokers and smokers with low to moderate dependence levels. Performances on cognitive tests were not correlated with the history of smoking or with the total exposure to tobacco measured as pack-years smoked. A third study found that among female twins ND was associated with low education, which is known to be correlated with low IQ [13].

Genetic factors are important in explaining IQ as well as ND. In adulthood, more than half of the variation in IQ is due to genetic differences between individuals [14]. For ND, heritability estimates have been reported in the range of 0.50–0.75 [15–18]. Even though smoking is associated strongly with socio-economic position in many societies, common genetic factors might also contribute to the association between IQ and ND.

Measures of ND are often based on cigarette smoking. However, in Sweden oral moist smokeless tobacco, snus, has become increasingly common during the past decades and today daily use of snus is more common (23%) than cigarette smoking (14%) among males [19]. Among young males aged 16–24 years, the difference is even larger (33% and 9%, respectively). One study also showed that 44% of Swedish male twins reported a combination of tobacco use from cigarettes and snus [20] and another study showed that dual users number as many as 55% [21]. When looking at level of nicotine from different sources in Sweden, Fagerström [22] reported that of the total amounts of nicotine consumed by males, 62.5% came from snus. The health effects of snus are not as clear as those of cigarette smoking. The few papers that have been published found an increased risk for pancreatic cancer, fatal myocardial infarction and stroke [23], CVD incidence [24] and major depression [25]. Another study found no association for non-fatal CVD or other types of cancer [26], Therefore, we did not find snus as interesting as smoking as a potential mediating factor of the association between intelligence and mortality. However, not accounting for use of snus when studying intelligence and ND would have biased the results, as dual use is a common phenomenon. Thus, ND from both cigarette smoking and snus use were analysed.

The aims of this study were (i) to investigate the correlation between IQ in young adulthood and ND in later life, and (ii) to investigate whether this correlation is due to common genetic or environmental factors.

MATERIAL

Target cohort and record-linkage of registers

Our target population consisted of all Swedish male twins born 1951–1984 who were identified in the Multi-Generation Register (MGR) [27] and in the Military Service Conscription Register (MSCR), including 29 524 twin individuals altogether. The MSCR provides information on all Swedish men eligible for conscription examination. During the years covered by this study (1969–2002), military conscription was compulsory for all Swedish men with the exception only of those with severe somatic or mental disabilities. Information about zygosity, smoking habits and the use of snus was obtained from the Swedish Twin Register (STR).

Measures of IQ

IQ was measured at military conscription at a mean age of 18.3 years [standard deviation (SD) 0.55 years]. During the study period, the IQ tests have changed three times. However, for this study we have used the standardized global IQ score, aiming to measure general ability, which means that any changes in number of items or subtests is unlikely to have biased the results. The first test was in use from 1969 to 1980 and the second from 1980 to 1994. Both have been described in more detail elsewhere [28,29]. They consisted of four subtests: logical, verbal, spatial and technical. The correlation between the tests is high. All tests were in the form of written questionnaires. The test that was used after 1994 was computer-based and consisted of 10 subtests instead of four and has been described in more detail elsewhere [30]. The aim of all tests, before and after 1994, was to measure general ability in order to judge the candidates' ability to undertake military service and the suitability for different duty positions [30]. All tests were standardized against the entire population of conscripts from the previous years to follow a Gaussian distribution between 1 and 9, with a mean of 5 and an SD of 2. A higher value indicates greater cognitive ability.

Measures of ND

Information about ND was collected through the STR and was based on two large twin surveys when the twins were 22–57 years of age. The first was the Screening Across the Lifespan Twin study (SALT). This screening covers twins born from 1900 to 1958. The study was initiated in 1998 with the purpose of screening for the most common complex diseases. It was conducted by a computer-assisted telephone interview between 1998 and 2002, in which older twins were interviewed first. The response rate for twins born 1926–1958 was 74%. The second was the Study of Twin Adults: Genes and

Environment (STAGE). It consisted of all twins in the Swedish Twin Registry born from 1959 to 1985 where both siblings were alive and living in the country. The purpose was, as for SALT, to screen for common complex diseases but also to evaluate relevant exposure in young adulthood and in midlife. It was conducted through a large web-based survey containing approximately 1300 questions. The response rate for STAGE was 60%, although it was lower for men (53%). Determination of zygosity in both SALT and STAGE was based on questions about childhood resemblance. In SALT the procedure was validated for a subsample with 13 DNA markers and found to be 99% accurate [31]. In STAGE a validation procedure was conducted with a panel of 47 single nucleotide polymorphisms in a random sample, and 95% were classified correctly [32]. More details about SALT and STAGE can be found in previously published work [31,33], including analysis of non-participation and generalizability [20,34]. The surveys included several sections of questions, where questions about tobacco use made up one section and questions about ND another.

There are two commonly used models to measure ND, where the first is a model of physical dependence, the FTND, and the other is based on psychiatric diagnostic tradition, DSM-IV. The FTND predicts smoking cessation (which is a key dimension of dependence) more accurately than DSM status. In this study ND was reported according to the FTND, which consists of a questionnaire with six items [35]. The FTND normally gives a score between 0 and 10. However, in our data one question (how soon after you wake up do you smoke your first cigarette?) had only three options instead of four (resulting in one score less); consequently, our scale ranged from 0–to 9 instead of 0 to 10.

In order to measure ND from snus, four questions were used on the use of snus similar to four of the questions in the FTND (details about the questions are available from the corresponding author upon request). Thus, the FTND score for snus ($FTND_{snus}$) ranged from 0 to 7. In the analyses we used both the traditional FTND score, the FTND score for snus and total ND as the higher of the two scores ($FTND_{total}$).

Measures of socio-economic position

Information about socio-economic position in childhood was based on parental occupation. It was assessed through Statistics Sweden's socio-economic index and was extracted from the Population and Housing Censuses when the participants were between 1 and 10 years of age. Parental occupational status was classified into six classes, from higher level non-manual to unskilled workers. Socio-economic position (SEP) in adulthood was measured by attained level of education and was extracted from the Longitudinal Database of Education, Income and Occupation (from 1990 to 2004). Level of education was classified into four categories, from 10 years of compulsory education to PhD education. Both measures were used as categorical variables in the regression models treating twins as individuals.

Table 1 Number of participants with information on available variables, means and standard deviations (SD).

	MZ		*DZ*	
	n	*Mean (SD)*	*n*	*Mean (SD)*
IQ	3736	5.2 (1.9)	9145	5.0 (1.9)
FTND	702	2.5 (1.8)	2241	2.5 (1.8)
$FTND_{snus}$	1075	2.1 (1.3)	3108	1.9 (1.3)
$FTND_{total}$	1281	2.5 (1.5)	3759	2.4 (1.7)

DZ: dizygotic; FTND: Fagerström Test for Nicotine Dependence; MZ: monozygotic.

Final study population

From the target population of 29 524 men, 2975 were excluded as they did not have information on IQ. This could have been due to not participating in the conscription examination, or participation in some parts but not the IQ test. Also for the years 1995–96, when the test changed from written questionnaire to a computerized test, there was a transitional period where data were lost. Another 10 965 men were excluded because they did not participate in any of the twin surveys, and 2703 men because of unknown zygosity. Furthermore, not everyone answered the questions about smoking and snus as they had never smoked or used snus ($n = 1631$) or had missing information ($n = 2694$), and not everyone answered the questions on ND ($n = 3516$). Consequently, the analyses were conducted on a study population of 5040 individuals, 2984 of them belonging to the older cohort (SALT) and 2056 belonging to the younger cohort (STAGE). Of these twin individuals, there were 807 complete twin pairs with information on IQ and either FTND or $FTND_{snus}$. Further details about the number of participants are given in Table 1.

METHODS

First, we analysed the association between IQ and ND among all twin individuals using a linear regression model. The analyses were performed with the Genmod procedure using SAS statistical software, version 9.1, using generalized estimating equations (GEE) to take into account the lack of statistical independence of twins within pairs. The analyses were additionally adjusted for birth year, parental occupation and own education.

Secondly, we looked at within-pair correlations of IQ and ND. Comparing these correlations for monozygotic (MZ) and dizygotic (DZ) twins provides an indication of the extent to which the association is influenced by genetic and/or environmental factors. If there were stronger correlations among MZ pairs than DZ pairs, it would indicate some genetic influences. If the correlations were similar and positive among both MZ and DZ, it would indicate no substantial genetic influences, but common environmental effects.

Finally, we used linear structural equation modelling to decompose the phenotypic variations in IQ and ND and the covariation between these traits. These models assume that the phenotypic variation is due to variation from additive genetic components (A), genetic dominance (D), common environment shared by twins (C) and unique environment factors specific to each twin individual (E), including measurement error [36]. However, in our model it was not possible to estimate D and C components simultaneously because all twins were reared together, which is why an ACE model was fitted to our data. The Mx and the Mplus statistical packages were used in these analyses [37]. First, univariate models for IQ and ND were fitted to the data. The univariate models were compared to saturated models to test the assumptions of equality of means and variances among MZ and DZ twins. The test value from the log-likelihood ratio test (LL), −2LL, related to degrees of freedom, and was used to identify the best-fitting univariate model used in subsequent analyses. Next, a bivariate Cholesky decomposition was fitted to the data in order to estimate the genetic and environmental correlations between IQ and ND. A Cholesky decomposition does not make any assumptions about the underlying genetic architecture but simply decomposes the variance and covariance into a series of uncorrelated genetic and environmental factors. All genetic analyses were adjusted for year of birth, as it showed statistically significant correlations with ND and global IQ ($r = 0.06$–0.32, $P < 0.0001$).

RESULTS

We used standardized values of each subtest as well as standardized values of global IQ. However, the results were almost identical for each of the four subtests (data not shown), and thus we decided to present analyses for only global IQ.

Table 1 presents means and SD for IQ and ND, together with the numbers of participating MZ and DZ twins. The association between IQ and ND was studied in linear regression models, corrected for the lack of statistical independence of twins within pairs. Table 2 shows regression coefficients for change in ND per 1-unit increase in IQ. The association was somewhat stronger for ND from cigarette smoking (FTND) than from snus use ($FTND_{snus}$) and total ND ($FTND_{total}$). In the model adjusted only for birth year (model A), a 1-unit increase in IQ resulted in a reduction of 0.13 [95% confidence interval (CI): −0.16, −0.09] in FTND on the 0–9 scale. The corresponding value for $FTND_{snus}$ was −0.04 (95% CI: −0.11, −0.07). Adjustment for parental occupation as well as own attained education attenuated the estimates, but still left statistically significant, albeit weak, associations.

Table 2 Association between intelligence quotient (IQ) and nicotine dependence from regression models, regression coefficients with 95% confidence intervals.

	Model A	*Model B*
FTND	−0.13 (−0.16, −0.09)	−0.07 (−0.11, −0.03)
$FTND_{snus}$	−0.04 (−0.06, −0.02)	−0.03 (−0.05, −0.01)
$FTND_{total}$	−0.09 (−0.11, −0.07)	−0.05 (−0.07, −0.02)

Model A was adjusted for birth year; model B was additionally adjusted for parental occupation and own education. FTND: Fagerström Test for Nicotine Dependence.

Next, we looked at intrapair correlations of IQ and ND in order to gain a first impression of any genetic influence on the association between IQ and ND, presented in Table 3. The overall phenotypic correlation for IQ and FTND was −0.095 ($P < 0.0001$). The within-pair correlation for IQ was 0.80 for MZ pairs and 0.52 for DZ pairs. ND correlated from 0.38 to 0.41 within MZ pairs and from 0.21 to 0.27 within DZ pairs. Within MZ pairs, the correlation between IQ and all measures of ND ranged from −0.08 to −0.19 and were statistically significant. Within DZ pairs, none of the correlations between IQ and ND were statistically significant. The results thus indicated a possible common genetic effect on these traits.

To address further the question about genetic influence on IQ and ND, we proceeded with quantitative genetic modelling. For IQ, dropping the common environment component decreased the model fit statistically significantly ($\Delta\chi^2_1 = 38.12$, $P = 0.0004$) and thus we used the ACE model. For ND, dropping the C component did not decrease the model fit for FTND ($\Delta\chi^2_1 = 1.38$, $P = 0.24$), $FTND_{snus}$ ($\Delta\chi^2_1 = 0$, $P = 1.00$) or $FTND_{total}$ ($\Delta\chi^2_1 = 0.74$, $P = 0.38$). However, as the lack of a statistically significant C component may also result from the lack of power, we decided to present the results of univariate models both for AE and ACE models. When comparing the fit of the best-fitting model to the saturated models, the model fit was good for IQ ($\Delta\chi^2_6 = 8.51$, $P = 0.20$) and all ND indicators ($\Delta\chi^2_7 = 3.86$–12.64, $P = 0.80$–0.08), indicating equality of means and variances by twin type. The heritability estimate (in the AE model) for all three types of ND were similar, for FTND it

Table 3 Intrapair and cross-twin cross-trait correlations of intelligence quotient (IQ), Fagerström Test for Nicotine Dependence (FTND) cigarette smoking, $FTND_{snus}$ and $FTND_{total}$, and number of complete pairs from which the correlation are computed.

MZ *Complete pairs* ↓	*Twin 1*↓ *Twin 2*→	*IQ*	*FTND*	*$FTND_{snus}$*	*$FTND_{total}$*
1760	IQ	0.80 ($n = 1760$)	–0.14 ($n = 350$)	–0.08 ($n = 518$)	–0.13 ($n = 617$)
170	FTND	–0.19 ($n = 318$)	0.38 ($n = 170$)	0.08 ($n = 153$)	0.35 ($n = 200$)
297	$FTND_{snus}$	–0.06 ($n = 497$)	0.24 ($n = 164$)	0.41 ($n = 297$)	0.30 ($n = 325$)
381	$FTND_{total}$	–0.15 ($n = 595$)	0.35 ($n = 217$)	0.24 ($n = 327$)	0.38 ($n = 381$)
DZ *Complete pairs* ↓	*Twin 1*↓ *Twin 2*→	*IQ*	*FTND*	*$FTND_{snus}$*	*$FTND_{total}$*
1831	IQ	0.52 ($n = 1831$)	–0.05* ($n = 480$)	0.07* ($n = 611$)	–0.03* ($n = 753$)
219	FTND	–0.05* ($n = 492$)	0.26 ($n = 219$)	0.18 ($n = 231$)	0.26 ($n = 283$)
308	$FTND_{snus}$	0.02* ($n = 626$)	0.16 ($n = 211$)	0.21 ($n = 308$)	0.20 ($n = 349$)
426	$FTND_{total}$	–0.04* ($n = 764$)	0.23 ($n = 276$)	0.23 ($n = 360$)	0.27 ($n = 426$)

*Non-significant correlations ($P > 0.05$). DZ: dizygotic; MZ: monozygotic; IQ: intelligence quotient.

Table 4 Proportions of variance of intelligence quotient (IQ), Fagerström Test for Nicotine Dependence (FTND), $FTND_{snus}$ and $FTND_{total}$ (ACE model) due to variation in additive genetic (a^2), common environmental (c^2) and unique environmental factors (e^2) in full models and the best-fitting univariate models (AE for nicotine dependence) with 95% confidence intervals.

		a^2	c^2	e^2
IQ	ACE	0.58 (0.52, 0.65)	0.22 (0.15, 0.28)	0.20 (0.19, 0.22)
	AE	–	–	–
FTND	ACE	0.21 (0.00, 0,47)	0.16 (0.00, 0.37)	0.63 (0.53, 0.75)
	AE	0.39 (0.29, 0,49)	–	0.61 (0.51, 0.71)
$FTND_{snus}$	ACE	0.32 (0.09, 0,41)	0.00 (0.00, 0.17)	0.68 (0.59, 0.78)
	AE	0.32 (0.23, 0,41)	–	0.68 (0.59, 0.77)
$FTND_{total}$	ACE	0.32 (0.09, 0.48)	0.08 (0.00, 0.26)	0.60 (0.52, 0.69)
	AE	0.42 (0.34, 0.48)	–	0.58 (0.52, 0.66)

ACE: additive genetic components (A), common environment shared by twins (C), environment factors specific to each twin individual (E).

was estimated to 0.39 (95% CI: 0.29–0.49) and for $FTND_{snus}$ and for $FTND_{total}$ the estimates were 0.32 (95% CI: 0.23–0.41) and 0.42 (95% CI: 0.34–0.48), respectively. If the ACE model was used, no statistically significant C component was found for FTND and $FTND_{total}$. All estimates are presented in Table 4.

The relative magnitude of genetic and environmental influences on the association of IQ and ND was estimated with bivariate Cholesky decomposition using the ACE model for IQ and nicotine dependence (Table 5). We found that common or specific environmental correlations were not statistically significant FTND (P values 0.794 and 0.605), $FTND_{snus}$ (P values 0.083 and 0.814) or $FTND_{total}$ (P values 0.889 and 0.394). The genetic correlation between FTND and IQ was –0.24 (95% CI: –0.52, 0.03). For $FTND_{total}$ and $FTND_{snus}$ the genetic correlation was –0.11 (95% CI: –0.24, –0.03) and –0.20 (95% CI: –0.40, –0.10), respectively.

Table 5 Trait correlations between intelligence quotient (IQ) and nicotine dependence and the correlation between additive genetic factors affecting these traits.

	Trait correlations (95% CI)	*Additive genetic correlations*[a] *(95%CI)*
IQ and FTND	–0.08 (–0.16, –0.01)	–0.24 (–0.52, –0.04)
IQ and $FTND_{snus}$	–0.09 (–0.15, –0.03)	–0.11 (–0.24, –0.03)
IQ and $FTND_{total}$	–0.11 (–0.16, –0.06)	–0.24 (–0.40, –0.10)

[a]Additive genetic correlations obtained from bivariate Cholesky decomposition. FTND: Fagerström Test for Nicotine Dependence; CI: confidence interval.

DISCUSSION

The aim of this study was to explore the association between IQ and ND and to analyse the mechanisms underlying this association. Linear regressions as well as

cross-twin, cross-trait correlations in both MZ and DZ twin pairs revealed weak associations between IQ and ND. The cross-twin, cross-trait correlations of IQ and ND were significant only within MZ pairs, indicating a possible genetic background. Our heritability estimate of 39% is somewhat lower than reported in most of the previous studies [15]; however, it is in line with those reported in a recent Finnish study [38], which found a heritability estimate of 0.40 (also using FTND). It is not clear why the heritability estimate of ND in our study, together with the Finnish study, was somewhat lower than previously published estimates; however, heritability estimates are population-specific. Possible explanations could be the high consumption of snus and the large proportion of dual users in Sweden. Also our population was young and the smoking prevalence lower than in the older cohorts. It is possible that when smoking becomes less common, it becomes more clustered within certain groups in the population [39,40]. If these groups tend to become more homogeneous (with respect to genetics and shared environment), genetic factors may explain less of the variation and environmental factors, primarily non-shared, become more important in explaining the variation.

We are not aware of any study exploring possible genetic overlap between IQ and ND. Azizian *et al.* [12] studied ND and performance on perceptual-motor tests of attention and argued that it is plausible that genetic mediators of cognitive difficulties might overlap with mediators of severity of ND. We found a weak support for this, with a genetic correlation between IQ and FTND of –0.18. Even though the heritability was almost equal for all three measures of ND, the trait correlation as well as the genetic correlation between IQ and $FTND_{snus}$ were lower than for IQ and FTND. However, the differences between the correlations were not statistically significant.

Under the circumstances described in the Introduction regarding the high number of snus users and dual users, it is essential to study ND from both cigarette smoking and snus use, especially as the questions in the FTND scale do not take into consideration nicotine intake from any source other than cigarettes. The scale that we used for snus is not validated. There are no good validated scales for ND from snus. However, Boyle *et al.* [41] have evaluated the FTND for smokeless tobacco in a US cohort and found that the total score correlated positively ($r = 0.47$) with serum cotinine in saliva. Ebbert *et al.* [42] also found a strong correlation with cotinine ($r = 0.53$) in another US cohort. In our study we used the same scale based on four questions, i.e. a reduced scale. However, not including any measures of ND from snus might have biased our results more than if we had included it. In addition, we presented the results from FTND, $FTND_{snus}$ and $FTND_{total}$ separately.

Twin studies need to make some assumptions and their violation affects results if not taken into account. We did not find any differences in means and SD between MZ and DZ twins, suggesting that there is no evidence that the sources of variation would differ between the zygosity groups. We did not have information on the parents of the twins, and thus we needed to make an assumption of random mating. A few studies have reported assortative mating with regard to smoking status [43,44]. If this is true for our population, and it is due to phenotypic assortment and not social homogamy, the DZ twins and their co-twins might share more than 50% of their segregating genes relevant to ND, and thus when comparing DZ and MZ twins the heritability will be underestimated. Conversely, assortative mating should increase the C component, but we found little evidence of that in this study. Further, we are not able to model gene–environment interactions or correlations separately, and thus the variance components estimated absorbed also these effects. Gene–environment interactions are modelled as part of genetic component if the environmental exposure is shared by the co-twins. Thus the lack of common environmental effect on ND does not mean that family environment could not affect ND; its effect may simply be modified by the genotype of the children. Further, the genetic effect may also include the effects of active or reactive gene–environment correlations; i.e. those with high ND may actively seek environments or evoke reactions from others which would increase their addiction further. A further limitation when studying ND is that we can only generalize our results to the exposed population, i.e. the individuals who have ever tried smoking or used snus.

The causal pathways between IQ and smoking status, smoking initiation or dependence are not well understood. Enhanced knowledge in this field may increase understanding of the IQ–mortality association, and improved knowledge about the pathways between IQ and smoking may also facilitate development of programmes for primary prevention and smoking cessation. In this study we found a weak phenotypic association and genetic correlation between IQ and ND, suggesting that ND is not an important mechanism of the association between IQ and smoking, nor an important mediator of the association between IQ and mortality.

CONCLUSION

Both IQ and ND from cigarette smoking and snus use showed moderate heritability, 0.58, 0.39 and 0.32, respectively. We found a weak phenotypic correlation between IQ and ND –0.11 (–0.16, –0.06) and bivariate analysis revealed very little genetic overlap between IQ and ND. ND does not seem to be a main explanatory

factor behind the established inverse association between IQ and smoking.

Declarations of interest

We have no conflicts of interest to declare. We are most grateful to the Swedish Twin Registry for making this study possible by providing access to an important dataset.

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References

1. Batty G. D., Deary I. J., Gottfredson L. S. Premorbid (early life) IQ and later mortality risk: systematic review. *Ann Epidemiol* 2007; **17**: 278–88.
2. Batty G. D., Wennerstad K. M., Smith G. D., Gunnell D., Deary I. J., Tynelius P. *et al*. IQ in early adulthood and mortality by middle age: cohort study of 1 million Swedish men. *Epidemiology* 2009; **20**: 100–9.
3. Deary I. J., Batty G. D. Cognitive epidemiology. *J Epidemiol Commun Health* 2007; **61**: 378–84.
4. Batty G. D., Deary I. J., Macintyre S. Childhood IQ in relation to risk factors for premature mortality in middle-aged persons: the Aberdeen Children of the 1950s study. *J Epidemiol Commun Health* 2007; **61**: 241–7.
5. Batty G. D., Deary I. J., Schoon I., Gale C. R. Mental ability across childhood in relation to risk factors for premature mortality in adult life: the 1970 British Cohort Study. *J Epidemiol Commun Health* 2007; **61**: 997–1003.
6. Hemmingsson T., Kriebel D., Melin B., Allebeck P., Lundberg I. How does IQ affect onset of smoking and cessation of smoking—linking the Swedish 1969 conscription cohort to the Swedish survey of living conditions. *Psychosom Med* 2008; **70**: 805–10.
7. Kubicka L., Matejcek Z., Dytrych Z., Roth Z. IQ and personality traits assessed in childhood as predictors of drinking and smoking behaviour in middle-aged adults: a 24-year follow-up study. *Addiction* 2001; **96**: 1615–28.
8. Taylor M. D., Hart C. L., Davey S. G., Starr J. M., Hole D. J., Whalley L. J. *et al*. Childhood mental ability and smoking cessation in adulthood: prospective observational study linking the Scottish Mental Survey 1932 and the Midspan studies. *J Epidemiol Commun Health* 2003; **57**: 464–5.
9. Taylor M. D., Hart C. L., Smith G. D., Starr J. M., Hole D. J., Whalley L. J. *et al*. Childhood IQ and social factors on smoking behaviour, lung function and smoking-related outcomes in adulthood: linking the Scottish Mental Survey 1932 and the Midspan studies. *Br J Health Psychol* 2005; **10**: 399–410.
10. Wennerstad K. M., Silventoinen K., Tynelius P., Bergman L., Kaprio J., Rasmussen F. Associations between IQ and cigarette smoking among Swedish male twins. *Soc Sci Med* 2010; **70**: 575–81.
11. Fergusson D. M., Horwood L. J., Ridder E. M. Show me the child at seven II: childhood intelligence and later outcomes in adolescence and young adulthood. *J Child Psychol Psychiatry* 2005; **46**: 850–8.
12. Azizian A., Monterosso J. R., Brody A. L., Simon S. L., London E. D. Severity of nicotine dependence moderates performance on perceptual-motor tests of attention. *Nicotine Tob Res* 2008; **10**: 599–606.
13. Kendler K. S., Neale M. C., Sullivan P., Corey L. A., Gardner C. O., Prescott C. A. A population-based twin study in women of smoking initiation and nicotine dependence. *Psychol Med* 1999; **29**: 299–308.
14. Plomin R., Spinath F. M. Intelligence: genetics, genes, and genomics. *J Pers Soc Psychol* 2004; **86**: 112–29.
15. Rose R., Broms U., Korhonen T., Dick D., Kim Y.-K., editors. *Genetics of Smoking Behaviour*. Chapter 28. *Handbook of Behaviour Genetics*. New York: Springer; 2009.
16. Maes H. H., Sullivan P. F., Bulik C. M., Neale M. C., Prescott C. A., Eaves L. J. *et al*. A twin study of genetic and environmental influences on tobacco initiation, regular tobacco use and nicotine dependence. *Psychol Med* 2004; **34**: 1251–61.
17. McGue M., Elkins I., Iacono W. G. Genetic and environmental influences on adolescent substance use and abuse. *Am J Med Genet* 2000; **96**: 671–7.
18. Vink J. M., Willemsen G., Boomsma D. I. Heritability of smoking initiation and nicotine dependence. *Behav Genet* 2005; **35**: 397–406.
19. Statistics Sweden. Living conditions, use of alcohol and tobacco, Report no 114. 2007.
20. Furberg H., Lichtenstein P., Pedersen N. L., Thornton L., Bulik C. M., Lerman C. *et al*. The STAGE cohort: a prospective study of tobacco use among Swedish twins. *Nicotine Tob Res* 2008; **10**: 1727–35.
21. Rosendahl K. I., Galanti M. R., Gilljam H. Trajectories of smokeless tobacco use and of cigarette smoking in a cohort of Swedish adolescents: differences and implications. *Nicotine Tob Res* 2008; **10**: 1021–7.
22. Fagerström K. The nicotine market: an attempt to estimate the nicotine intake from various sources and the total nicotine consumption in some countries. *Nicotine Tob Res* 2005; **7**: 343–50.
23. Boffetta P., Straif K. Use of smokeless tobacco and risk of myocardial infarction and stroke: systematic review with meta-analysis. *BMJ* 2009; **339**: b3060.
24. Yatsuya H., Folsom A. R. Risk of incident cardiovascular disease among users of smokeless tobacco in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 2010; **172**: 600–5.
25. Edwards A. C., Maes H. H., Pedersen N. L., Kendler K. S. A population-based twin study of the genetic and environmental relationship of major depression, regular tobacco use and nicotine dependence. *Psychol Med* 2011; **41**: 395–405.
26. Boffetta P., Hecht S., Gray N., Gupta P., Straif K. Smokeless tobacco and cancer. *Lancet Oncol* 2008; **9**: 667–75.
27. Statistics Sweden. Multi-generation register 2004—a description of contents and quality. 2003:5.1. 2005.
28. Carlstedt B., Mardberg B. Construct validity of the Swedish Enlistment Battery. *Scand J Psychol* 1993; **34**: 353–62.
29. Carlstedt B. Cognitive abilities—aspects of structure, process and measurement. Göteborg Studies in Educational Sciences 148. *Acta Universitas Gothoburgensis*, 2000.
30. Mardberg B., Carlstedt B.; Swedish Enlistment Battery (SEB). Construct validity and latent variable estimation of

cognitive abilities by the CAT-SEB. *Int J Sel Asses* 1998; **6**: 107–14.
31. Lichtenstein P., de Faire U., Floderus B., Svartengren M., Svedberg P., Pedersen N. L. The Swedish Twin Registry: a unique resource for clinical, epidemiological and genetic studies. *J Intern Med* 2002; **252**: 184–205.
32. Frisell T., Lichtenstein P., Rahman Q., Langstrom N. Psychiatric morbidity associated with same-sex sexual behaviour: influence of minority stress and familial factors. *Psychol Med* 2010; **40**: 315–24.
33. Lichtenstein P., Sullivan P. F., Cnattingius S., Gatz M., Johansson S., Carlstrom E. *et al*. The Swedish Twin Registry in the third millennium: an update. *Twin Res Hum Genet* 2006; **9**: 875–82.
34. Furberg H., Lichtenstein P., Pedersen N. L., Bulik C., Sullivan P. F. Cigarettes and oral snuff use in Sweden: prevalence and transitions. *Addiction* 2006; **101**: 1509–15.
35. Heatherton T. F., Kozlowski L. T., Frecker R. C., Fagerstrom K. O. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 1991; **86**: 1119–27.
36. Boomsma D., Busjahn A., Peltonen L. Classical twin studies and beyond. *Nat Rev Genet* 2002; **3**: 872–82.
37. Neale M. C., Boker S., Xie G., Maes H. *Mx Statistical Modelling*, 6th edn. Richmond, VA: Virginia Commonwealth University, Department of Psychiatry; 2002.
38. Broms U., Madden P. A., Heath A. C., Pergadia M. L., Shiffman S., Kaprio J. The nicotine dependence syndrome scale in Finnish smokers. *Drug Alcohol Depend* 2007; **89**: 42–51.
39. Broms U., Silventoinen K., Lahelma E., Koskenvuo M., Kaprio J. Smoking cessation by socioeconomic status and marital status: the contribution of smoking behavior and family background. *Nicotine Tob Res* 2004; **6**: 447–55.
40. Jefferis B. J., Power C., Graham H., Manor O. Changing social gradients in cigarette smoking and cessation over two decades of adult follow-up in a British birth cohort. *J Public Health (Oxf)* 2004; **26**: 13–18.
41. Boyle R. G., Jensen J., Hatsukami D. K., Severson H. H. Measuring dependence in smokeless tobacco users. *Addict Behav* 1995; **20**: 443–50.
42. Ebbert J. O., Patten C. A., Schroeder D. R. The Fagerstrom Test for Nicotine Dependence–Smokeless Tobacco (FTND-ST). *Addict Behav* 2006; **31**: 1716–21.
43. Boomsma D. I., Koopmans J. R., Van Doornen L. J., Orlebeke J. F. Genetic and social influences on starting to smoke: a study of Dutch adolescent twins and their parents. *Addiction* 1994; **89**: 219–26.
44. Vink J. M., Willemsen G., Boomsma D. I. The association of current smoking behavior with the smoking behavior of parents, siblings, friends and spouses. *Addiction* 2003; **98**: 923–31.