Prenatal exposure to tobacco and future nicotine dependence: population-based cohort study

Mina Rydell, Sven Cnattingius, Fredrik Granath, Cecilia Magnusson and Maria Rosaria Galanti

Background
Maternal smoking during pregnancy may increase the risk of nicotine dependence, especially in girls, but data are conflicting and confounding by other familial factors cannot be ruled out.

Aims
To clarify the relationship between prenatal tobacco exposure and adolescent tobacco uptake and dependence in boys and girls respectively, while taking confounding factors into close consideration.

Method
We conducted a prospective longitudinal study, comprising 3020 Swedish youths followed from 11 to 18 years of age. Exposure and outcome information was elicited via self-administered parental and repeated youth questionnaires. Hazard ratios (HRs), odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated as measures of associations.

Results
Girls prenatally exposed to maternal tobacco use had a two- to threefold increased odds of experiencing a high number of withdrawal symptoms (OR = 2.83, 95% CI 1.68–4.87), craving for tobacco (OR = 2.04, 95% CI 1.28–3.32) and heavy tobacco use (five or more cigarettes or snus dips per day) (OR = 1.93, 95% CI 1.30–2.86). These associations were weaker among boys, and did not reach formal statistical significance. Associations between prenatal tobacco exposure and onset of regular tobacco use in both genders appeared to be mostly explained by parents' social position and postnatal smoking behaviour.

Conclusions
Prenatal exposure to tobacco is linked to an increased risk of nicotine dependence among adolescent girls.

Declaration of interest
M.R.G. is responsible for the tobacco prevention activities carried out by the Department of Public Health Sciences on behalf of Stockholm County Council. F.G. participates in a study funded by Pfizer, aimed at studying the potential adverse birth outcomes of varenicline. This project is a part of fulfilling the US Food and Drug Administration/European Medicines Agency's requirement of post-marketing surveillance and has no link to the presented work.

Knowledge about determinants of tobacco use and of nicotine dependence is required for effective tobacco control. Prenatal exposure to tobacco has been implicated as such a determinant, since nicotine crosses the placenta barrier, and can result in even higher fetal than maternal blood concentrations. Nicotine acetylcholine receptors are present in the fetal brain from the fourth week of gestation onwards, and it has been suggested that exposure to nicotine can lead to sensitisation and early disruption of acetylcholine-mediated pathways (teratogenesis). Ultimately, these functional and perhaps morphological changes could result in an enhanced vulnerability to tobacco dependence. This hypothesis is supported by findings from animal studies, and from studies on human cell systems.

However, neurological teratogenesis is not the only mechanism by which prenatal tobacco exposure may be linked to tobacco use and/or nicotine dependence later in life. The causal model presented in Fig. 1 posits that maternal tobacco use can be associated with use and dependence through: (a) a common genetic liability; (b) direct behavioural influence of parental postnatal tobacco use; and (c) influence from common social factors on both maternal and children's behaviour. In light of the complexity of this causal model, it is not surprising that the few existing studies of tobacco uptake have yielded inconsistent results, including reports of positive, null or even inverse associations. Stronger evidence of a positive and causal association have, however, been found in relation to nicotine dependence. Our understanding of the potential brain priming impact of fetal nicotine exposure is thus hampered by incomplete control of confounding in prior studies. In addition, there are no data on smokeless tobacco use, either as a source of prenatal exposure to nicotine or as an offspring outcome.

The primary purpose of this study, based on a large prospective cohort of youths, was to clarify whether there is an association between prenatal tobacco exposure and risk of tobacco use and dependence during adolescence, after controlling for the influence of parental postnatal tobacco use as well as familial social position. Secondarily, we wanted to assess whether such an association differs between genders. In fact, animal studies indicated a stronger effect of prenatal exposure to nicotine among females, while previous epidemiological studies were inconsistent.

Study population
The BROMS (Children’s Smoking and Environment in Stockholm County) cohort study was conducted in Stockholm County between 1998 and 2005, with the main purpose of studying development and determinants of tobacco use in adolescence. The study was approved by the ethical board at Huddinge University Hospital and has been described in detail elsewhere. Briefly, 3020 children recruited during the fifth grade of compulsory school (average age 11 years) were followed until 3 years after compulsory school (average 18 years), resulting in one baseline assessment and six follow-up surveys. At each survey, the children reported their past and current tobacco use by means of a structured questionnaire. The annual participation rate ranged from 87 to 96%, with 69% of the adolescents participating in all surveys. At baseline, the children’s parents were also asked to complete a questionnaire eliciting information on parental characteristics (participation rate 99%).
Measure

Exposure
Information regarding prenatal exposure to tobacco was reported from parents at baseline. The mother and father were separately asked whether they smoked or used snus (the Swedish form of moist oral snuff) when the mother was pregnant with the index child. Parental tobacco use was investigated according to both timing (use during the first or second/third trimesters of pregnancy) and frequency (daily or occasional).

Prenatal tobacco exposure from the maternal source was defined as the mother’s self-reported use of any tobacco (cigarettes and/or snus), categorised as: any, none. As very few mothers changed their tobacco use during the pregnancy, duration of use was not considered.

Furthermore, we considered the cumulative passive exposure to the fetus, deriving from maternal tobacco use and from paternal smoking, resulting in one variable with four mutually exclusive categories:
(a) exposure from both parents (father smoked at least occasionally during the index pregnancy and mother smoked and/or used snus at least occasionally);
(b) exposure to maternal tobacco use only (mother smoked and/or used snus at least occasionally, while father did not use tobacco at all, or only used snus);
(c) exposure to paternal smoking only (father smoked at least occasionally, while mother did not use tobacco at all);
(d) no prenatal exposure to tobacco use from parental source (no maternal use of tobacco, no paternal smoking).

If non-use of tobacco was reported by a parent during the first trimester of pregnancy, missing information during the second and third trimester was categorised as non-use, since initiation of tobacco use during pregnancy is very rare. Incomplete information regarding either mother’s or father’s use of tobacco during pregnancy was coded as missing for the combined measure of parental tobacco use. Due to missing values, 142 study participants were excluded from analyses where maternal tobacco use during pregnancy was used as the exposure variable and 327 participants were excluded from analysis where any prenatal tobacco exposure from a parental source (i.e. using information on both maternal and paternal tobacco use) was used.

Outcome
Outcome measures included: onset of any current use and of daily use of tobacco during follow-up; lifetime experience of intense craving for tobacco; lifetime experience of withdrawal symptoms in case of discontinuation of tobacco use; and total current tobacco consumption. The latter three outcomes were based on reports elicited at the age of 17 years.

Onset of tobacco use. Combining answers from survey questions, an average index of total annual consumption was calculated separately for cigarettes and snus. Two outcome variables were analysed for each type of tobacco: onset of any current use (having smoked at least 12 cigarettes or used at least 12 snus dips during the year preceding the survey); and onset of daily use (at least 240 cigarettes or snus dips during the year preceding the survey). Children who were current users at baseline (n = 10), and those who did not take part in any follow-up survey (n = 9) were excluded from the analyses of onset of tobacco use.

Measures of nicotine dependence and withdrawal symptoms. The study population for the analysis of these outcomes consisted of adolescents who reported any current use of tobacco and who participated in the survey conducted at the age of 17 years (2 years after compulsory school) when the assessment of nicotine dependence and withdrawal symptoms was conducted for the first time. Details regarding this assessment have been reported previously. Among the items used to identify nicotine dependence included in the survey, we restricted the current analyses to lifetime reports of intense urge to use tobacco (craving). In fact, craving has been found to occur early and frequently in adolescents’ smoking trajectories, and to be independent of withdrawal symptoms. In addition, it has been argued that the presence of this symptom is sufficient to make a diagnosis of nicotine dependence, based on a neurobehavioural model predicting drug administration and escalation.

The following withdrawal symptoms after discontinued tobacco use were investigated: craving, feeling upset or tense, impaired concentration, feeling depressed, increased appetite/weight, heart palpitation, nausea, anxiety and sleeping problems (all categorised as yes v. no). An index of these items was created, and dichotomised as experienced four or more symptoms v. fewer, based on the median value. The number of symptoms in this analysis represents a conservative estimate because of partially missing answers.

Tobacco consumption. A variable for total tobacco consumption at age 17 was derived, in order to distinguish between high (at least five cigarettes and/or snus dips per day), low (less than five cigarettes and/or snus dips per day) and no consumption.

Other covariates
Postnatal exposure to parental tobacco use was assessed through the children’s surveys between the ages of 11 and 14 years (baseline
through follow-up wave three). Answers obtained separately for each parent were combined into a summary variable where a child was considered exposed to postnatal tobacco use if the child at any time point recalled either parent using any type of tobacco. Missing information on no more than two occasions, in combination with reports of non-use on the other occasions, was regarded as parental non-use. Apart from this instance, a combination of negative and missing information for any variable was generally categorised as missing.

Family’s socioeconomic position was assessed through self-reported information on parental occupation and education. Occupation was coded according to the Swedish socioeconomic classification from Statistics Sweden. Parental education, defined as the number of years each parent had attended school, was categorised as compulsory (≤ 9 years), intermediate (10–12 years) or high (> 12 years). For the purpose of this study, the mother’s occupation and education were primarily used. We also analysed a combined measure of higher education for both parents, coded as: both parents, either parent or neither with college education.

Information on parents’ country of birth was reported by the children at baseline and categorised as both parents, either parent or neither born in a Nordic country (i.e. Sweden, Denmark, Finland, Iceland and Norway). Childhood health events that may have influenced tobacco habits were obtained through reports from school nurses. For this analysis, we used information on diagnoses of asthma and allergies (coded as yes v. no).

### Statistical analyses

Study populations and analytical samples for the outcomes included in this analysis are reported in Table 1. SAS version 9.2 for Windows was used for all analyses. Onset of tobacco use was analysed by means of Cox regression, with failure time corresponding to the year during which monthly or daily use was first reported. Follow-up time in absence of failure was considered exposure if the child at any time point recalled either parent using any type of tobacco. Missing information on no more than two occasions, in combination with reports of non-use on the other occasions, was regarded as parental non-use. Apart from this instance, a combination of negative and missing information for any variable was generally categorised as missing.

Adjustments were made for potential confounders following the causal model illustrated in Fig.1. In brief, social characteristics assumed to have a direct or indirect effect on the child’s tobacco use and nicotine dependence, as well as the child’s health, were considered potential confounders. In multivariate models, we only adjusted for those characteristics that were associated with the respective outcomes in univariate models and modified the crude association between exposure and outcome by at least 10%.

All analyses were done separately among boys and girls. Analyses of snus uptake were restricted to boys, since such uptake was rare in girls.

### Results

Sociodemographic characteristics of the study population are shown in Table 2. The majority of the study participants were 11 years or younger at baseline, and had highly educated parents.

<table>
<thead>
<tr>
<th>Table 1: Analytical samples employed for the various study outcomes</th>
<th>Analytical sample, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 1467, Female 1411</td>
</tr>
<tr>
<td>Maternal education</td>
<td>Compulsory 328, Intermediate 1089, High 1403</td>
</tr>
<tr>
<td>Maternal occupation</td>
<td>Unskilled worker 378, Skilled worker 256, Low-level clerk 457, Middle-level clerk 763, High-level clerk 406, Self-employed 129, Not in the labour force 313</td>
</tr>
<tr>
<td>Parents’ country of birth</td>
<td>Both parents 2304, One parent 230, Neither parent 236</td>
</tr>
<tr>
<td>Parents’ postnatal tobacco use</td>
<td>Never 1277, Ever 1446</td>
</tr>
</tbody>
</table>

### Table 2: Prevalence of prenatal tobacco exposure in relation to baseline characteristics

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>Prenatally exposed to maternal use of tobacco, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1467</td>
<td>27.3</td>
</tr>
<tr>
<td>Female</td>
<td>1411</td>
<td>27.4</td>
</tr>
<tr>
<td>Age</td>
<td>11 years or younger 2480, 12 years or older 398</td>
<td>26.9, 30.2</td>
</tr>
<tr>
<td>Maternal education</td>
<td>Compulsory 328, Intermediate 1089, High 1403</td>
<td>43.6, 33.1, 19.5</td>
</tr>
<tr>
<td>Parents with college education</td>
<td>None 971, One 734, Both 928</td>
<td>36.8, 26.7, 15.1</td>
</tr>
<tr>
<td>Parents’ born in the Nordic countries</td>
<td>Both parents 2304, One parent 230, Neither parent 236</td>
<td>28.4, 27.7, 16.5</td>
</tr>
<tr>
<td>Parents’ postnatal tobacco use</td>
<td>Never 1277, Ever 1446</td>
<td>9.8, 44.3</td>
</tr>
</tbody>
</table>

*P*-value for χ² test < 0.001.

b. Parents’ postnatal tobacco use includes any parental smoking or snus use during the index child’s age of 11-14 years.
Discussion

In this large prospective study we found clear associations between maternal tobacco use during pregnancy and nicotine dependence as well as heavy smoking among adolescent girls – but not boys. These findings were robust, also when important confounding factors including parental social position and postnatal tobacco use were accounted for. However, prenatal exposure to tobacco was not linked to onset of regular tobacco use in adolescence in a straightforward way. In fact, the association appeared to be confined to boys, and was as strong for maternal as for paternal sources, probably indicating residual confounding. These results are compatible with the theoretical model in Fig.1, postulating social influences as the main causal pathway to substance use initiation, while the importance of intra-uterine exposure would be revealed in the clinical manifestation of dependence (such as strong urge to use tobacco and heavy consumption).

All previous studies where nicotine dependence was analysed in relation to prenatal exposure to maternal smoking showed associations of direction and magnitude very similar to ours. We add to this knowledge that the strength of withdrawal symptoms appears associated with prenatal exposure to tobacco in a dose–response fashion.

The lack of a clear association between prenatal exposure to tobacco and daily smoking in our study was rather surprising, as onset of daily smoking is an obvious indication of progression in smoking behaviour, which may be related to early onset of dependence. In fact, the majority of earlier studies did report such an association, although others did not present inconsistent results. However, our findings regarding the risk of high tobacco consumption in late adolescence suggest that transition to more established and regular tobacco use (as opposed to initial episodes of tobacco use) is associated with prenatal exposure to tobacco, which is in line with previous results.

Comparison of findings between our and other studies is hampered by differences in study designs and population characteristics. For instance, many studies reporting an association between prenatal tobacco exposure and tobacco use in offspring were based on relatively small and/or high-risk samples of pregnant mothers, with low retention at follow-up in some instances even based on reports from the offspring, thus potentially being prone to recall bias. In addition, differences in ages and outcome definition may have contributed to discrepancies. In our analysis, spanning from early to late adolescence, daily tobacco use was categorised as average use of 20 cigarettes or snus per day, whereas no association was evident among boys. Having experienced four or more withdrawal symptoms after discontinuation of tobacco use was more common among children prenatally exposed to maternal tobacco use had twofold higher adjusted odds of feeling a strong urge to use tobacco (craving), while no association was evident among boys.

Having experienced four or more withdrawal symptoms after discontinuation of tobacco use was more common among children prenatally exposed to maternal tobacco use compared with those unexposed (Table 4). Separate analyses by gender again showed statistically significant associations only among girls, with ORs of 3.28 if both parents used tobacco, and of 2.30 if only the mother did, but no association with paternal smoking only.

Table 5 shows the adjusted ORs of being a low (less than five cigarettes and/or snus per day) or heavy consumer (five or more cigarettes and/or snus per day) of tobacco at the age 17 of years. After adjusting for parental postnatal use of tobacco and parental education, girls prenatally exposed to maternal tobacco use had twofold increased odds of being heavy consumers of tobacco compared with girls unexposed to maternal tobacco use, whereas no such an association could be found in boys. Prenatal tobacco exposure was not associated with low consumption of tobacco.
<table>
<thead>
<tr>
<th>Table 3</th>
<th>Hazard ratios (HRs) and corresponding confidence intervals (CIs) of onset of daily smoking during adolescence in relation to parental tobacco use during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Cases</td>
<td>Crude HR 95% CI</td>
</tr>
<tr>
<td>Maternal tobacco use during pregnancy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>519 1.00 1.00</td>
</tr>
<tr>
<td>Any</td>
<td>264 1.76 1.51–2.06</td>
</tr>
<tr>
<td>Parental tobacco use during pregnancyb</td>
<td></td>
</tr>
<tr>
<td>No parental use</td>
<td>319 1.00 1.00</td>
</tr>
<tr>
<td>Both maternal tobacco use and paternal smoking</td>
<td>146 2.12 1.73–2.60</td>
</tr>
<tr>
<td>Only maternal tobacco use</td>
<td>87 1.75 1.37–2.24</td>
</tr>
<tr>
<td>Only paternal smoking</td>
<td>123 1.35 1.09–1.67</td>
</tr>
<tr>
<td>a. Adjusted for parental postnatal tobacco use during the index child's age of 11–14 years (any v. none) and for parents with college education (none, one or both).</td>
<td></td>
</tr>
<tr>
<td>b. Some cases exposed to maternal tobacco use are missing because of missing information on paternal smoking.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Odds ratios (ORs) and corresponding confidence intervals (CIs) of lifetime experience of symptoms of nicotine dependence and withdrawal at age 17 in relation to parental tobacco use during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>Cases</td>
<td>Crude OR 95% CI</td>
</tr>
<tr>
<td>Craving/strong urge</td>
<td></td>
</tr>
<tr>
<td>Maternal tobacco use during pregnancy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>303 1.00 1.00</td>
</tr>
<tr>
<td>Any</td>
<td>195 1.78 1.33–2.40</td>
</tr>
<tr>
<td>Parental tobacco use during pregnancyb</td>
<td></td>
</tr>
<tr>
<td>No parental use</td>
<td>211 1.00 1.00</td>
</tr>
<tr>
<td>Both maternal tobacco use and paternal smoking</td>
<td>107 1.62 1.12–2.37</td>
</tr>
<tr>
<td>Only maternal tobacco use</td>
<td>64 2.10 1.29–3.50</td>
</tr>
<tr>
<td>Only paternal smoking</td>
<td>79 0.89 0.62–1.28</td>
</tr>
<tr>
<td>At least four withdrawal symptoms (v. fewer than four)</td>
<td></td>
</tr>
<tr>
<td>Maternal tobacco use during pregnancy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>253 1.00 1.00</td>
</tr>
<tr>
<td>Any</td>
<td>161 1.86 1.34–2.59</td>
</tr>
<tr>
<td>Parental tobacco use during pregnancyb</td>
<td></td>
</tr>
<tr>
<td>No parental use</td>
<td>163 1.00 1.00</td>
</tr>
<tr>
<td>Both maternal tobacco use and paternal smoking</td>
<td>93 2.19 1.29–2.93</td>
</tr>
<tr>
<td>Only maternal tobacco use</td>
<td>49 2.14 1.25–3.76</td>
</tr>
<tr>
<td>Only paternal smoking</td>
<td>78 1.35 0.91–2.02</td>
</tr>
<tr>
<td>a. Adjusted for parental postnatal tobacco use during the index child's age of 11–14 years (any v. none) and for parents with college education (none, one or both).</td>
<td></td>
</tr>
<tr>
<td>b. Some cases exposed to maternal tobacco use are missing because of missing information on paternal smoking.</td>
<td></td>
</tr>
</tbody>
</table>
Boys vs Highb vs Lowb

### Table 5

<table>
<thead>
<tr>
<th>Cases OR 95% CI</th>
<th>Lowb vs no</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
<th>OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal tobacco use during pregnancy</td>
<td>None</td>
<td>1.00</td>
<td>225</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Any</td>
<td>1.07</td>
<td>0.85–1.34</td>
<td>1.46</td>
<td>1.12</td>
</tr>
<tr>
<td>Parental tobacco use during pregnancy</td>
<td>Both maternal tobacco use and paternal smoking</td>
<td>1.20</td>
<td>0.83–1.72</td>
<td>2.12</td>
<td>1.12</td>
</tr>
<tr>
<td></td>
<td>Only maternal tobacco use</td>
<td>1.03</td>
<td>0.74–1.42</td>
<td>1.43</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>Only paternal smoking</td>
<td>1.03</td>
<td>0.79–1.39</td>
<td>1.46</td>
<td>1.03</td>
</tr>
</tbody>
</table>

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**Strengths and limitations**

This study has several strengths. First, it was based on a large longitudinal sample with high retention at follow-up. Prenatal exposures were assessed prospectively and outcomes were assessed through repeated measurements over 7 years. Recognising that maternal smoking may not be the only source of tobacco toxicants to the fetus, we also included information on maternal snus use and paternal smoking during the index pregnancy (as a possible source of passive prenatal tobacco exposure). Although the distant recall of pregnancy tobacco use by the parents might have introduced some misclassification, a validation study among mothers of the children in the BROMS cohort showed good concordance with self-reports of smoking elicited during pregnancy. This good concordance is further supported by findings from an American study that showed high congruency between retrospective reports of pregnancy smoking, prospective reports and levels of urinary cotinine. Likewise, a validation study of a subsample of this cohort’s participants showed a 98% concordance between self-reported no use of any tobacco in the past month and cotinine concentration in saliva, with a sensitivity of 90% and specificity of 93%. Finally, we could adjust for major confounders chosen a priori, according to a theoretical model. Parental use of tobacco during childhood and adolescence is one of the factors with the strongest impact on adolescent smoking, probably acting through both role modelling and availability of tobacco. In this study, we took advantage of repeated reports on parents’ tobacco use as experienced by their children (i.e., the final target of social influences).

Some limitations should be kept in mind when interpreting our results. Children of highly educated parents born in Nordic countries were overrepresented, because of initial selection owing to parental consent. This may have affected the power of the study to detect weak associations, because of low rates of daily smoking among children. However, if parents’ social status were a moderator of the effect of prenatal exposure to tobacco, the bias...
introduced by this selection would most likely result in under-
estimation of the association under study. We could not adjust
for other potential confounders such as parenting style, parental
comorbidity, exposure to passive smoking as an infant,36 other
eye life influences and genetic liability to nicotine dependence,
well documented in previous studies on twins.7 However, the
gender differences found in our study would suggest genetic
confounding to have a minor role.

Findings from this study indicate that symptoms of nicotine
dependence and progression in tobacco use in adolescent girls
can be linked with nicotine exposure in utero. This suggests that
nicotine dependence should be added to the risks of passive
dependence and progression in tobacco use in adolescent girls.

First received 25 Jul 2011, final revision 10 Oct 2011, accepted 11 Nov 2011

Acknowledgements

We are grateful to Simon Lind, Peeter Fredlund and Gunilla Björklund for assistance with
data analysis.

Mina Rydell, MSc, Department of Public Health Sciences, Karolinska Institutet;
Sven Cnattingius, PhD, Fredrik Granath, PhD, Department of Medicine, Karolinska
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Funding

This study was funded with grant 2008-0876 from the Swedish Council for Working Life
and Social Research. The BRUMS Cohort Study was funded with grant 346/2002-36 from the
Swedish Research Council and by the Stockholm County Council. Study sponsors had no
role in the design and conduct of the study, collection, management, analysis and
interpretation of the data, or preparation, review or approval of the manuscript.

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Coming to Terms with Schizophrenia

Barry Tebb

Why our son, why?
Every morning the same dark chorus wakes me
And I wonder how I am still alive.

‘Balance the forces of life and death’
Is the Kleinian recipe for survival.

‘It is God’s will, life is meant to test us’
My Christian heritage tells me.

‘Life is a vale of soul making’
Keats reminds us.

Insistently the morning traffic hums
As I sip my tea, list calls to make,
Sigh in frustration at unread books.

For solace I look at cards of Haworth
Moorland vistas of unending paths
Cloudscapes only a Constable could paint
High Withens in a gale, the sloping village street.

How? When? Why?
‘The truth’ – if such an entity exists –
is that I want to run away

Barry Tebb was born in Leeds in 1942. He is a carer and a prolific poet, Leeds Partnerships NHS Foundation Trust governor and campaigner for better mental health. This poem is from Tranquillity Street: New & Selected Poems, published by Sixties Press in 2004 and reprinted with permission.

Chosen by Femi Oyebode.

Prenatal exposure to tobacco and future nicotine dependence: population-based cohort study
Mina Rydell, Sven Cnattingius, Fredrik Granath, Cecilia Magnusson and Maria Rosaria Galanti
Access the most recent version at DOI: 10.1192/bjp.bp.111.100123

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