Smoking tobacco is associated with renal hyperfiltration

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ABSTRACT

Tobacco consumption is a renal risk factor, but the effects on the estimated glomerular filtration rate (eGFR) remain unclear. We aimed to evaluate the possible impact of using tobacco products (smoking and snus) on eGFR based on creatinine or cystatin C. We used a first cohort with 949 participants and a second cohort with 995 participants; none had pre-existing renal disease. All subjects donated a blood sample and completed a questionnaire, including questions about tobacco use. To assess the effect on eGFR, hierarchical multiple linear regression models were used. Active smoking associated independently with a higher eGFR\textsubscript{creatinine} in all subjects (\(p < 0.001; \beta = 0.11\)). Further analyses stratified for sex, showed similar findings for men (\(p < 0.001; \beta = 0.14\)) and for women (\(p = 0.026; \beta = 0.10\)). eGFR\textsubscript{cystatin C} was significantly associated with active smoking in all subjects (\(p = 0.040; \beta = -0.05\)), but no association was seen after stratification for sex. Snus did not associate with eGFR. In conclusion, smoking associated significantly with a higher eGFR\textsubscript{creatinine}. The mechanism may be renal hyperfiltration of smaller molecules such as creatinine. This is probably caused by substances from smoked tobacco other than nicotine, as no effect was seen for snus.

Introduction

The detrimental effects of tobacco consumption are well known. Smoking is a significant risk factor for multiple diseases, such as atherosclerosis, cancer, and chronic respiratory disease. [1,2]. The World Health Organization (WHO) estimated that tobacco products were responsible for about 8 million premature mortalities worldwide in 2017 [3]. Furthermore, the usage of tobacco products is still one of the leading causes of premature death and global disease burden [4].

There is also evidence suggesting that smoking has a negative impact on renal function. Harmful outcomes such as the increased risk for end-stage renal failure in renal patients, progression of nephropathies, and diabetic nephropathy in people with diabetes are all relatively well-documented effects of smoking [5]. Smoking is thus an established renal risk factor in individuals already diagnosed with renal disease. However, in individuals without pre-existing renal disease, previous studies have been more inconclusive.

Studies investigating the effect of tobacco products on eGFR in individuals independent of pre-existing renal disease are conflicting. Several studies have reported that smoking is associated with a decreased eGFR or an increased risk of developing chronic kidney disease (CKD) in healthy subjects [6–10]. Others have reported an association with an increased eGFR [11–15]. This is pathophysiologically important since an increased eGFR, also called glomerular hyperfiltration, is associated with increased cardiovascular risk, carotid plaques, diabetes, and obesity [16–20].

Few studies have investigated the effects of both smoking and snus consumption; in the study by Ekberg et al., smoking was associated with a higher GFR, whereas no association was seen for snus [21]. It is thus unknown if tobacco products other than smoking are associated with altered renal function.

Both creatinine and cystatin C are filtered over the glomerular membrane in the kidney with different size-dependent sieving coefficients and both can reliably be used to calculate the estimated glomerular filtration rate (eGFR).

The aim of this study was to evaluate if there was a difference in the association of smoked tobacco and consumption of snus on eGFR in subjects without pre-existing renal disease. Another aim was to see if there was a difference between eGFR\textsubscript{creatinine} and eGFR\textsubscript{cystatin C}. To assess this, we...
used healthy controls from two previous population-based studies [22,23].

**Material and methods**

**Study population**

The participants in this study were all part of the Northern Sweden Health and Disease Study (NSHDS) that includes the Västerbotten Intervention Project (VIP), Mammography screening program (MA), and the Northern Sweden WHO Monitoring of Trends and Cardiovascular Disease (MONICA). These population-based cohorts have previously been evaluated [24].

VIP is an ongoing project offering a systematic screening of risk factors and subsequent health counselling to all residents in Västerbotten county since 1985. The program is offered annually to all residents upon turning 30 (until 1995) 40, 50, and 60 and is previously described in detail [25]. In MONICA, seven health surveys have been performed between 1986 and 2014 with randomly selected individuals in Västerbotten and Norrbotten counties aged 25 to 74 years [26]. The MA cohort includes women aged 40 to 70 who were invited to the cohort while undergoing routine mammography between 1995–2006. Added together, these cohorts included 140,414 participants up to December 2014, with an estimated participation rate of 65–75%.

In all three cohorts, the participants are asked to complete a questionnaire covering tobacco habits and to donate a blood sample to the Northern Sweden Medical biobank for future research. The clinical examinations conducted at inclusion have recently been described in detail [27].

The study was approved by the regional ethical board, Umeå, Sweden (Dnr 03-320, Dnr 07-174 M, Dnr 2014-348-32 M). All participants gave their informed written consent before inclusion in the NSHDS, and the study complied with the Declaration of Helsinki.

**Identification of participants**

We used the matched controls from two prospective case–control studies nested within the NSHDS cohort [22,23]. Cases in the first study were first-time myocardial infarction (fatal or nonfatal) or suspected MI that occurred prior to 1 January 2000. Two controls were matched for sex, age, geographic area, subcohort, and date of the health survey. Controls were excluded if they had cancer, stroke or myocardial infarction prior to the matched case time of diagnosis. A total of 1054 controls were selected, of which 77 were excluded because of missing tobacco status and/or eGFR variable, and 28 because they used both snus and smoking tobacco, leaving 995 individuals for analysis. No exclusions were done in the second cohort due to previous cardiovascular disease or cancer. A flowchart for both studies is shown in Supplementary Figure 1.

Diabetes was defined according to WHO guidelines as either self-reported diabetes or fasting plasma glucose ≥7.0 mmol/L and/or an oral glucose tolerance test with a 2-h postload plasma glucose ≥11.0 mmol/L (12.2 mmol/L in VIP as capillary plasma was used). Smoking habits were self-reported and were categorized by whether the participants used tobacco products daily (smoking or snus) or not (including earlier tobacco use and never tobacco-users).

**Sample collection and biochemical analysis**

Venous blood samples were obtained after at least 4 h of fasting (extended to 8 h after 1992) in the VIP and MONICA projects. In MA, the samples were obtained throughout the day. Blood samples were drawn into evacuated glass tubes and centrifuged for 15 min at 1500 g to get heparinized plasma, which was aliquoted and stored at −80°C before analysis.

Plasma samples were analyzed at Umeå University Hospital, Department of Clinical Chemistry, Sweden accreditation no 1397. In the first cohort, creatinine and cystatin C were analyzed with a Hitachi 911 multi analyzer (Roche/Boehringer Mannheim, Germany). Creatinine was analyzed with kits from Roche, Crea plus, enzymatic method (Creatinine kit Cat. No. 11775669216), and creatinine results were IDMS-corrected. Cystatin C (Cat. No LX 00210, calibrator X097401) was analyzed with kits from DAKO (Copenhagen, Denmark). In the second cohort, creatinine and cystatin C were analyzed on a Cobas 8000 modular analyzer, c502 module (Roche Diagnostics, Basel, Switzerland). Creatinine was analyzed with an IDMS traceable enzymatic method, CREP2 (catalogue no. 03263991190) and cystatin C with Tina-quant cystatin C Gen. 2 traceable to the ERMDA471/IFCC standard (catalogue no. 06600239190 [23]). Both these kits were from Roche Diagnostics (Basel, Switzerland).

Estimated glomerular filtration rate (eGFR) was calculated using the revised Lund-Malmö estimating equation for eGFR<sub>creatinine</sub> according to the following equations [28]; Female and plasma creatinine (pCr) < 150 = 2.50 + 0.0121 × (150 − pCr); Female and pCr ≥ 150 = 2.50 − 0.926 × ln(pCr/150); Male and pCr < 180 = 2.56 + 0.00968 × (180 − pCr); and Male and pCr ≥ 180 = 2.56 − 0.926 × ln(pCr/180). This equation outperforms MDRD and CKD-EPI in a Swedish population [29]. For eGFR<sub>cystatinC</sub>, the Caucasian, Asian, Pediatric, Adult cohorts (CAPA) equation was used, according to the following equation; eGFR = 130 × cystatinC − 1.069 × age − 0.117 − 7 [30].

**Statistical analysis**

Baseline characteristics were presented as medians (25th to 75th percentiles) for continuous variables and non-continuous
variables as proportions/percent. We used Mann–Whitney U-test for continuous variables and a Chi-squared test for independence for categorical variables to compare baseline characteristics in different tobacco groups. P-values < 0.05 were considered significant.

We calculated ln z-scores for eGFRcreatine and eGFRcystatin C, which was done separately for the two cohorts and also separately for men and women. The two cohorts were then merged into one. For assessment of smoking, a hierarchical multiple regression model was used to predict eGFRcreatine and eGFRcystatin C levels. The predictor variables were tobacco status (current smoker or nontobacco user) and age were entered into the model in step 1. Sex, systolic blood pressure (mm Hg), BMI (body mass index), diabetes and study (first or second) were added into the model in step 2. Participants with missing data points were excluded pairwise. Preliminary analyses were carried out to ensure that assumptions of sample size, outliers, multicollinearity, linearity, normality, and homoscedasticity were not violated.

For snus consumption, a similar hierarchical multiple regression model was used to predict eGFRcreatine and eGFRcystatin C levels. However, the predictor variable ‘tobacco status’ was defined as current snus user or non-tobacco user.

All calculations were performed with SPSS version 27 (IBM Corporation, New York, NY, USA).

### Results

Baseline characteristics for the first (n = 949) and second (n = 995) cohorts are shown in Tables 1 and 2. In the first cohort, both snus users and active smokers had higher eGFRcreatine than nontobacco users. Stratified for sex, this finding was also seen in men and for smoking women eGFRcystatin C was lower in smokers compared to nontobacco users. Snus users had a higher eGFRcystatin C compared to both smokers and nontobacco users. These findings were also seen for men. In the second cohort, eGFRcreatine was higher in smokers than non-tobacco users after stratification for sex. This was also seen for all snus users, although not significant for men (p = 0.06). Men using snus had lower eGFRcreatine compared to smokers. eGFRcystatin C did not differ between smokers and nontobacco users. In the second cohort, eGFRcystatin C was not higher among snus users.

#### Hierarchical multiple regression models for smoking and z-scores of ln eGFRs

For all subjects, current smoking (compared to not currently using tobacco products) and age were entered in Step 1, explaining 22% of the variance in eGFRcreatine and 14% of the variance in eGFRcystatin C (Supplementary Table 1). Smoking associated with increasing eGFRcreatine (p < 0.001; β = 0.11), whereas no association was seen for cystatin C. In step 2, sex, BMI, diabetes, systolic blood pressure and cohort were added. This model explained the variance in eGFRcreatine by 24% and 17% in eGFRcystatin C. Smoking still associated with increasing eGFRcreatine (p < 0.001; β = 0.11). In contrast, smoking associated with a lower eGFRcystatin C but only in step 2 (p < 0.040; β = −0.05). As sex was a significant predictor for eGFR, further analyses were stratified for sex, showing similar findings. In men, smoking associated significantly with increasing eGFRcreatine (p < 0.001; β = 0.14) in Step 1 (Table 3). After adjustments in step 2, smoking remained associated with increasing eGFRcreatine (p < 0.001; β = 0.14). This was not seen for eGFRcystatin C. In women, smoking remained associated with increasing eGFRcreatine after adjustments in step 2 (p = 0.026; β = 0.10). As for men, no association between smoking and eGFRcystatin C was seen for women.

### Table 1. Baseline characteristics of participants in the first cohort, stratified for tobacco status.

| Variable               | Nontobacco users | Smokers       | p-value (nontobacco users vs smokers) | Nontobacco users | Smokers       | p-value (nontobacco users vs smokers) | p-value (smokers vs nontobacco users) |
|------------------------|------------------|---------------|--------------------------------------|------------------|---------------|--------------------------------------|---------------------------------------|
| n                      | 699              | 147           | 0.375                                               | 103              |               | <0.001                                                | <0.001                                                         |
| Sex (M/F)              | 467/232          | 92/55         | 0.434                                               | 50.2 (43.5; 59.7) |               | <0.001                                                | <0.001                                                         |
| Age at sample donation (years) | 59.2 (50.0; 60.1) | 58.8 (50.1; 60.0) | 0.001                                               | 50.2 (43.5; 59.7) |               | <0.001                                                | <0.001                                                         |
| Age men (years)        | 53.9 (49.9; 60.0) | 50.2 (49.9; 60.0) | 0.759                                               | 50.1 (43.4; 59.7) |               | 0.001                                                | 0.025                                                         |
| Lovee age women (years) | 60.0 (52.8; 64.8) | 59.8 (52.5; 60.2) | 0.106                                               | N/A              |               | N/A                                                | N/A                                                         |
| BMI                    | 25.5 (23.6; 27.8) | 24.7 (23.0; 27.4) | 0.019                                               | 25.7 (22.9; 27.8) | 0.727         | 0.198                                                | N/A                                                          |
| Diabetes (%)           | 5.1              | 6.6           | 0.663                                               | 4.3              | 0.938         | 0.668                                                | 0.482                                                         |
| SBT                    | 133.2 (122.5;144.9) | 125.6 (121.4;140.4) | 0.002                                               | 131.4 (122.5;140.4) | 0.042 | 0.482                                                | N/A                                                          |
| eGFRcreatine (ml/min/1.73m²) | 88.6 (82.3; 95.6)  | 92.0 (86.1; 98.5) | 0.001                                               | 91.3 (86.4; 99.0) |               | <0.001                                                | <0.001                                                         |
| all                    | 90.2 (83.8; 97.1)  | 93.1 (86.2; 99.9) | 0.012                                               | 91.3 (86.4; 99.0) | 0.031         | 0.707                                                | <0.001                                                         |
| men                    | 85.9 (79.5; 92.8)  | 91.1 (85.4; 97.8) | 0.001                                               | 95.2              | N/A           | N/A                                                | N/A                                                          |
| eGFRcystatin C (ml/min/1.73m²) | 82.0 (72.3; 92.2)  | 79.0 (70.2; 87.3) | 0.052                                               | 86.2 (77.9; 98.9) | 0.003 | 0.004                                                | <0.001                                                         |
| all                    | 82.3 (73.2; 92.5)  | 79.6 (71.8; 88.4) | 0.247                                               | 86.2 (77.9; 99.0) | 0.014         | 0.004                                                | <0.001                                                         |
| women                  | 80.14 (70.9; 90.5) | 78.1 (68.7; 86.2) | 0.121                                               | 94.5              | N/A           | N/A                                                | N/A                                                          |

Medians (25th to 75th percentiles) for continuous variables Percent/percentages for noncontinuous variables. P-values < 0.05 are shown in bold. N/A = not applicable. BMI = body mass index (kg/m²); Diabetes defined as fasting plasma glucose ≥7.0 mmol/L and/or post-load plasma glucose ≥ 11.0 mmol/L (12.2 mmol/L if capillary); SB = systolic blood pressure (mm Hg).
Table 2. Baseline characteristics of participants in the second cohort, stratified for tobacco status.

| Variable          | Nontobacco users | Smokers | p-value (nontobacco users vs smokers) | Snus users | p-value (nontobacco users vs snus users) | p-value (smokers vs snus users) |
|-------------------|------------------|---------|--------------------------------------|------------|----------------------------------------|-------------------------------|
| Sex               | 716              | 170     | <0.001                               | 109        | N/A                                    | N/A                           |
| Age at sample     | 59.8 (50.1; 60.2)| 50.8    | 0.001                                | 50.2       | 0.001                                  | <0.001                        |
| Age donation(years) | 25.7 (23.6; 28.1)| 24.6    | 0.005                                | 26.5       | 0.001                                  | <0.001                        |
| BMIc              | 4.1              | 3.8     | 0.004                                | 1.00       | N/A                                    | N/A                           |
| eGFRcreatinine (ml/min/1.73m²) | 80.0 (73.4; 86.7) | 85.6 (78.1; 93.5) | <0.001                               | 83.2       | 0.001                                  | 0.133                         |
| eGFRcystatin C (ml/min/1.73m²) | 90.9 (80.6; 102.0) | 89.3 (79.0; 101.9) | 0.598                               | 92.5       | 0.289                                  | 0.199                         |

Medians (25th to 75th percentiles) for continuous variables. Percent/Proportions for noncontinuous variables. P-values < 0.05 are shown in bold. N/A = not applicable. BMI = body mass index (kg/m²); Diabetes defined as fasting plasma glucose ≥ 7.0 mmol/L and/or postload plasma glucose ≥ 11.0 mmol/L (12.2 mmol/L if capillary); SBT = systolic blood pressure (mm Hg).

Table 3. Associations of smoking with eGFRcreatinine and eGFRcystatin C stratified for sex.

| Predictor variable | eGFRcreatinine | eGFRcystatin C |
|--------------------|----------------|---------------|
|                     | B              | SE B          | Beta/β | sr  | P     | R²   | ΔR² | B              | SE B          | Beta/β | sr  | P     | R²   | ΔR² |
| Men                |                |               |        |     |       |      |     |                |               |        |     |       |      |     |
| Constant           | 3.04           | 0.19          | <0.001 |     |       |      |     | 2.29           | 0.20          | <0.001 |     |       |      |     |
| Smoking            | 0.37           | 0.07          | 0.14   | 0.14| <0.001|      |     | −0.13          | 0.08          | −0.05  | −0.05| 0.09  |      |     |
| Age                | −0.06          | <0.01         | −0.47  | −0.47| <0.001|      |     | −0.04          | <0.01         | −0.36  | −0.35| <0.001|      |     |
| Women              |                |               |        |     |       |      |     |                |               |        |     |       |      |     |
| Constant           | 3.43           | 0.31          | <0.001 |     |       |      |     | 2.44           | 0.32          | <0.001 |     |       |      |     |
| Smoking            | 0.37           | 0.08          | 0.14   | 0.14| <0.001|      |     | −0.15          | 0.08          | −0.06  | −0.06| 0.06  |      |     |
| Age                | −0.06          | <0.01         | −0.45  | −0.43| <0.001|      |     | −0.04          | <0.01         | −0.34  | −0.33| <0.001|      |     |

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In total, only six women were using snus combining both cohorts; thus, the analyses were only conducted for men. Snus usage (compared to not currently using tobacco products) did not associate with eGFRcreatinine or eGFRcystatin C (Supplementary Table 2).

Discussion

The main finding in our study was that active smoking independently associated with increasing eGFRcreatinine after adjustments, an association seen in both men and women. In contrast, smoking associated inversely with eGFRcystatin C although not in the stratified analysis for sex. Snus did not associate with eGFR.
Little is known about tobacco consumption and its effect on renal function in individuals without pre-existing renal disease. Both an increased eGFR [11–15], decreased eGFR [6,8,10], or a decreased measured GFR (mGFR) [7] have been proposed in previous studies. A higher eGFR, has previously been called renal hyperfiltration since a higher prevalence of proteinuria has been found simultaneously [12–14].

Some previous studies have reported an effect of current smoking for both men and women on eGFR, but with a more pronounced effect for men [12,13], and some studies included only men [14,15]. In our study, active smoking was still associated with a higher eGFRcreatinine in both sexes after including factors previously associated with renal hyperfiltration [18–20,31] such as age, BMI, diabetes and systolic blood pressure.

To our knowledge, all previous studies on the consumption of tobacco reporting an increased eGFR only evaluated eGFRcreatinine and not eGFRcystatin C [11–15] or used measured mGFR based on cr-EDTA clearance [21]. In our study, we both eGFRcreatinine and eGFRcystatin C. One study reported a decreased GFR and a higher risk for renal function decline based on MAG3-clearance but not for mGFR based on DTPA-clearance [7]. Other studies measured urinary albumin excretion [9], or when using eGFR, followed the participants for five to ten years until developing CKD [6,8], thus possibly missing the early phase of renal disease. Renal hyperfiltration might be a marker of early glomerular damage, supported by a recent systematic review suggesting that ‘glomerular hyperfiltration is thought to play an important role in the initiation of glomerular damage’ [32]. Renal hyperfiltration has also been associated with increased cardiovascular risk, carotid plaques, rapid decline in renal function in people with diabetes, obesity and other metabolic parameters [16–20].

A possible mechanism behind the difference in eGFRcreatinine and eGFRcystatin C results is the difference in cystatin C and creatinine molecular size, affecting the filtration in the renal glomeruli. This has been described as ‘shrunken pore syndrome’, defined as eGFRcystatin C being 60% lower than eGFRcreatinine [33]. Interestingly, this has also been associated with several health consequences similar to those associated with renal hyperfiltration, such as; increased mortality [34], aortic stenosis with concomitant atherosclerosis [23], as well as with accumulation of atherosclerosis promoting proteins [35] and increased risk of a future first-ever myocardial infarction in women [36].

In addition, recent studies have shown that eGFR equations based on plasma levels of cystatin C are outperforming eGFR equation based on creatinine in predicting outcomes such as; end-stage renal failure, all-cause mortality, cardiovascular disease, CKD in the elderly, and glomerular filtration rate in people with diabetes [37–41]. Partly suggesting a greater accuracy of cystatin C than creatinine as a filtration marker, but on the other hand, it has also been shown that eGFR is associated with many cardiovascular and mortality risk factors independent of mGFR [42–45]. This indicates that eGFRs are not only markers for glomerular filtration but are also biomarkers dependent on cardiovascular risk factors, including smoking. These different factors more often affect eGFRcystatin C than eGFRcreatinine. This might also explain the mechanisms behind the atherogenic potential of smoking and the tight relationship between CKD and CVD. Another possible explanation behind the increased eGFRcreatinine results seen in smokers would be that smokers might have a lower muscle mass due to an overall lower level of fitness. This would also explain why eGFRcystatin C are similar or lower in smokers, since cystatin C does not depend on muscle mass. In our study, we did not measure muscle mass. However, BMI did not differ between smokers and non-smokers in the first cohort, but we found a difference in the second. When stratified for sex, no difference in BMI was seen in the first cohort. In the second cohort significantly lower BMI was seen for female smokers only (data not shown). However, since BMI does not take into consideration body composition and is not a reliable measurement of muscle mass, we can not conclude whether the higher eGFRcreatinine found in smokers is dependent on muscle mass.

It is unclear if tobacco products other than smoking affect GFR since we could only find one study assessing snus consumption [21]. This study reported no significant effect on mGFR in 13 snus users, which we could confirm in our study assessing 206 male oral snus users. Unfortunately, our cohorts did not include a sufficient number of women consuming snus to determine the effects on eGFRs in women. Some experimental studies have shown reduced glomerular filtration after nicotine administration, indicating that not only smoking but all kind of nicotine administration influences glomerular filtration [46], but this was only seen in healthy non-smokers and not in chronic smokers. In our study, the null finding for snus users indicates that substances other than nicotine in smoked tobacco influence eGFR, as the nicotine metabolite cotinine has been shown to be higher among snus users than smokers [47].

The main strength of the study is that the participants are from cohorts that are evaluated as population-based [24]. VIP has also been evaluated in participation trends, showing minimal differences in, e.g. age and education between participants and non-participants, and no declining participation rate [48]. We also used traceable creatinine and cystatin C methods, and creatinine was analyzed with an enzymatic method not sensitive for pseudocreatinines.

Our study has several limitations. Firstly, smoking has been associated with eGFR in a dose-dependent manner [10,11]. However, we could not assess a dose-dependent association between tobacco and eGFR since we did not have sufficient information about the amount of tobacco consumed in our participants. Secondly, our study did not include a sufficient number of smokers to stratify into current smokers, ex-smokers, and nonsmokers and still retain statistical power, making it impossible to draw conclusions whether the effects of smoking on eGFR are reversible upon smoking cessation. On the other hand, it has been stated that eGFR was significantly higher in current smokers (both light and heavy smokers) compared to both ex-smokers and
non-smokers [11,14], indicating a reversible effect. Another limitation was that the analysis of creatinine and cystatin C were performed at different time points and for cystatin C with different methods. To minimize the effect of this we used z-scores derived from the first and second cohort separately.

In conclusion, we provide evidence that smoking contributes significantly to a higher eGFRcreatinine in men and women. The mechanism behind this association might be renal hyperfiltration of smaller molecules, including creatinine, as this was not seen for the larger molecule, cystatin C. This is probably caused by substances from smoked tobacco other than nicotine, as no effect was seen for snus. Further longitudinal studies, including both eGFRcreatinine and eGFRcystatin C, are needed to determine the effects of different distribution routes of tobacco on eGFR, including possible dose-dependency and reversibility upon smoking discontinuation.

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Data availability statement

Aggregate data are included in the manuscript and its Supporting Information files.

The data that support the findings of this study are available on request from the Northern Sweden Health and Disease Study Biobank. To request data, interested researchers must complete a formal application (available at https://www.umu.se/en/biobank-research-unit/research/access-to-samples-and-data/access-to-nsdd/) and submit it to The Biobank Research Unit at Umeå University (contact via ebf@umu.se). Individual data are not publicly available due to containing information that could compromise the privacy of research participants.

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