

## **ONLINE SUPPLEMENTARY INFORMATION to Snus in pregnancy and infant birth size; a mother-child birth cohort study**

### **Methods**

Inclusion criteria were singleton and twin pregnancies at week 16-22 and sufficient Scandinavian language skills. Upon primary enrolment the women were informed about how to complete the 18- and 34-weeks electronic questionnaires.

Although we had available birth weight and tobacco exposure for the excluded infants born before gestational week 35, we chose not to include them because of potential bias such as severe disease.

Twin pregnancies were excluded mainly because their mean birth weight of 2682 grams was significantly different (p-value <0.000) from the singletons' mean weight of 3582 grams.

The Standard Operating Procedures for anthropometric measurements were based upon a pilot where different measuring methods were tested. We chose the procedures that were easiest to perform and had the highest inter-rater reliability.

### **Discussion**

In the entire cohort with available GA at birth (both included and non-included in this study), there was no significant difference between tobacco exposure groups when separated into preterm (GA <37 weeks) and term (GA ≥37 weeks) delivered babies (eTable S2). In addition, of the 10 excluded preterm infants born before gestational week 35, only one was exposed to snus during pregnancy, making the exposure in this group considered the same as for the rest of the cohort.

There are limitations related to the timing and method of the biometric measure used in the routine ultrasound scan conducted between weeks 16-22 as the basis for GA identification. Ultrasound measures in the first trimester are supposed to be more reliable at identifying gestational age due to lower biological variation in fetal size. Femur length was the standardized measure in all study sites and therefore used to estimate GA as the biometric measures of the fetal head circumference were assessed differently in Sweden and Norway.

**Table S1 Baseline characteristics of the study population**

		PreventADALL cohort; twins excluded n=2688		
		Completed 18 and/or 34 W Q n=2515		
		Included	Not included in the	
Background characteristics	No.	N=2313	mother-child cohort	P-value
			N=202	
<b>Fetal sex, male no. (%), no. (%)</b>	2313	1216 (52.6)	-	
<b>GA at birth, mean (no.)</b>	2347			
	Weeks	39.3 (1.7)	38.2 (2.3)	<0.001
	Days	274.8 (11.7)	267.3 (16.0)	<0.001
<b>Maternal factors, mean (SD)</b>				
	Age - years	2515 32.4 (4.1)	32.2 (4.5)	0.37
	Pre-pregnancy BMI	2450 23.1 (3.6)	23.5 (4.2)	0.15
	Height - cm	2480 168.0 (6.2)	167.8 (6.4)	0.63
	Weight before pregnancy - kg	2461 65.4 (11.2)	66.2 (12.3)	0.33
	Weight at inclusion - kg	2488 70.1 (11.2)	70.8 (12.4)	0.43
	18w BMI	2478 24.8 (3.7)	25.2 (4.2)	0.23
<b>Pregnancy history, no. (%)</b>				
Current in vitro fertilization	2501			0.91
	Yes	177 (7.7)	15 (7.5)	
Previous miscarriage(s) <12w	2501			
	0	1737 (75.2)	149 (74.1)	0.45
	1	408 (17.7)	41 (20.4)	
	>1	165 (7.1)	11 (5.5)	
Previous late miscarriage/stillbirths 12-23w	2501			0.91
	0	2250 (97.8)	197 (98.0)	
	1	48 (2.1)	4 (2.0)	
	>1	2 (0.1)	0 (0.0)	
Parity	2337			
	0	1290 (60.0)	114 (61.0)	0.31
	1	677 (31.5)	63 (33.7)	
	>1	183 (8.5)	10 (5.3)	
<b>Sociodemographic factors, no. (%)</b>				
Education	2328			0.57
	Preliminary school only	16 (0.7)	2 (1.1)	
	High school only	219 (10.2)	18 (9.6)	
	Higher education <4 years	682 (31.9)	70 (37.4)	
	Higher education ≥4 years	1222 (57.1)	97 (51.9)	
	Other	2 (0.1)	0 (0.0)	
Country of origin	2337			0.10
	Norway and Sweden	1914 (89.0)	159 (85.0)	
	Rest of the world	236 (11.0)	28 (15.0)	
Marital status	2337			0.020
	Married	885 (41.2)	77 (41.2)	
	Cohabitants	1210 (56.3)	99 (52.9)	
	Single	37 (1.7)	5 (2.7)	

	Divorced/separated	1 (0.0)	0 (0.0)	
	Other	17 (0.8)	7 (3.2)	
Living area		2337		0.17
	City, densely populated	834 (38.8)	76 (40.6)	
	City, less densely populated	817 (38.0)	60 (32.1)	
	Suburb	343 (16.0)	29 (15.5)	
	Countryside, village	111 (5.1)	16 (8.6)	
	Countryside, outside village	46 (2.1)	6 (3.2)	
Household income		2337		0.15
	Low	25 (1.2)	5 (2.7)	
	Middle	1150 (53.5)	108 (57.8)	
	High	938 (43.6)	70 (37.4)	
	Not reported	37 (1.7)	4 (2.1)	
<b>Smoking history, no. (%)</b>				
Previous smoking		2337	475 (22.1)	54 (28.9)
In utero exposure to cigarette smoking		2337		0.56
	No	1623 (75.5)	137 (73.3)	
	Yes	306 (14.2)	32 (17.1)	
	Do not know	221 (9.5)	18 (9.6)	

No.=number, SD=standard deviation, g=grams, BMI=body mass index, kg=kilogram, w=week, pop=populated

**Table S2: Tobacco exposure among term ( $\geq 37$  weeks) and preterm infants ( $< 37$  weeks)**

**All subjects in the PreventADALL cohort (except twins) included at 18W with available gestational age (GA) and questionnaire (n=2347)**

	Total	Never	Tobacco exposure during pregnancy		P-value
			Snus only	Smoke/dual	
Preterm* no. (%)	281 (100)	250 (89.0)	13 (4.6)	18 (6.4)	0.103
Term no. (%)	2066 (100)	1834 (88.8)	144 (7.0)	88 (4.3)	

\*Preterm: infants born  $< 37$  weeks.

**Table S3. Results on building the multivariable linear regression models to determine significant covariates for the final model of each outcome.** Significance level: 5 per cent.

Outcomes	Covariates	
	Non-significant	Significant
Abdominal circumference/Head circumference	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area Pre-pregnancy BMI GA at birth	Parity Fetal sex Maternal age
Thoracic circumference/Abdominal circumference	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area Pre-pregnancy BMI Parity Fetal sex Maternal age	GA at birth
Thoracic circumference/Head circumference	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area Pre-pregnancy BMI	GA at birth Parity Fetal sex Maternal age
Birth weight/placenta weight	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area Pre-pregnancy BMI	GA at birth Parity Fetal sex Maternal age
Upper left arm circumference	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area	GA at birth Parity Fetal sex Maternal age Pre-pregnancy BMI
Abdominal circumference	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area	GA at birth Parity Fetal sex Maternal age Pre-pregnancy BMI
Length	Previous smoking history Maternal education In utero exposure to tobacco Marital status Maternal age	GA at birth Parity Fetal sex Pre-pregnancy BMI Living area
Birth weight	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area	GA at birth Parity Fetal sex Maternal age Pre-pregnancy BMI
Head circumference	Previous smoking history Maternal education In utero exposure to tobacco Marital status Living area Maternal age	GA at birth Parity Fetal sex Pre-pregnancy BMI
Thoracic circumference	Previous smoking history	GA at birth

Placenta weight

Maternal education  
In utero exposure to tobacco  
Marital status  
Living area  
Previous smoking history  
Maternal education  
In utero exposure to tobacco  
Marital status  
Maternal age

Parity  
Fetal sex  
Pre-pregnancy BMI  
Maternal age  
GA at birth  
Parity  
Fetal sex  
Pre-pregnancy BMI  
Living area

**Table S4. Linear regression analyses: Effect of tobacco exposure during pregnancy on anthropometric measures (cm).** The reference group ‘Never’ includes all women who did not report use of tobacco or nicotine during pregnancy. The ‘Smoke/dual’ group includes dual smokers and snus users during pregnancy of who most quit before 6 weeks of pregnancy.

Tobacco exposure during pregnancy	No.	B	95% CI	P-value	No.	B	95% CI	P-value	
									<b>Length</b>
		<b>Univariable</b>			<b>Multivariable (1-4, 6)</b>				
								0.27	0.37
Never	1718	Ref.			1718	Ref.			
Snus	137	0.28	(-0.09, 0.64)		137	0.24	(-0.10, 0.58)		
Smoke/dual	93	-0.13	(-0.57, 0.31)		93	0.04	(-0.37, 0.44)		
								0.44	
Never	1718	Ref.			1718	Ref.		0.49	
Snus only up to 18w	128	0.26	(-0.12, 0.64)		128	0.28	(-0.07, 0.63)		
Snus only up to 34w	9	0.47	(-0.91, 1.9)		9	-0.06	(-1.3, 1.2)		
Smoke/dual	93	-0.13	(-0.57, 0.31)		93	0.04	(-0.37, 0.44)		
<b>Head circumference</b>									
		<b>Univariable</b>			<b>Multivariable* (1-4)</b>				
								0.023	0.023
Never	1762	Ref.			1762	Ref.			
Snus	143	0.34	(0.10, 0.60)		143	0.32	(0.09, 0.55)		
Smoke/dual	95	0.017	(-0.28, 0.32)		95	0.097	(-0.18, 0.38)		
								0.041	<b>0.055</b>
Never	1762	Ref.			1762	Ref.			
Snus only up to 18w	132	0.31	(0.06, 0.57)		132	0.31	(0.07, 0.55)		
Snus only up to 34w	11	0.71	(-0.14, 1.57)		11	0.41	(-0.39, 1.2)		
Smoke/dual	95	0.017	(-0.28, 0.32)		95	0.10	(-0.18, 0.38)		
<b>Head circumference sensitivity analyses</b>									
		<b>Univariable</b>			<b>Multivariable (1-4, 7)</b>				
								0.014	0.053
Never	1684	Ref.			1684	Ref.			
Snus	137	0.37	(0.12, 0.62)		137	0.29	(0.06, 0.53)		
Smoke/dual	88	0.004	(-0.31, 0.31)		88	0.03	(-0.26, 0.32)		
								0.024	0.108
Never	1684	Ref.			1684	Ref.			
Snus only up to 18w	127	0.34	(0.08, 0.60)		127	0.28	(0.03, 0.53)		
Snus only up to 34w	10	0.81	(-0.09, 1.7)		10	0.47	(-0.37, 1.3)		
Smoke/dual	88	0.004	(-0.31, 0.31)		88	0.03	(-0.26, 0.32)		
<b>Thoracic circumference</b>									
		<b>Univariable</b>			<b>Multivariable (1-5)</b>				



				0.28			0.27
Never	1710	Ref.			1710	Ref.	
Snus	136	0.23	(-0.10, 0.56)		136	0.18	(-0.13, 0.49)
Smoke/dual	89	0.19	(-0.21, 0.60)		89	0.23	(-0.15, 0.61)
				0.43			0.26
Never	1710	Ref.			1710	Ref.	
Snus only up to 18w	126	0.25	(-0.09, 0.60)		126	0.23	(-0.09, 0.55)
Snus only up to 34w	10	-0.03	(-1.21, 1.16)		10	-0.46	(-1.56, 0.64)
Smoke/dual	89	0.19	(-0.21, 0.60)		89	0.23	(-0.15, 0.61)

#### Abdominal circumference

	Univariable			Multivariable (1-5)			
				0.69			0.75
Never	1709	Ref.			1709	Ref.	
Snus	136	0.09	(-0.29, 0.47)		136	0.07	(-0.30, 0.43)
Smoke/dual	89	-0.16	(-0.63, 0.30)		89	-0.15	(-0.59, 0.30)
				0.86			0.85
Never	1709	Ref.			1709	Ref.	
Snus only up to 18w	126	0.08	(-0.31, 0.48)		126	0.09	(-0.29, 0.47)
Snus only up to 34w	10	0.14	(-1.20, 1.49)		10	-0.23	(-1.52, 1.05)
Smoke/dual	89	-0.16	(-0.63, 0.30)		89	-0.15	(-0.59, 0.30)

#### Left upper arm circumference

	Univariable			Multivariable (1-5)			
				0.13			0.13
Never	1718	Ref.			1718	Ref.	
Snus	136	0.19	(0.01, 0.37)		136	0.18	(0.00, 0.35)
Smoke/dual	88	0.04	(-0.19, 0.26)		88	0.04	(-0.17, 0.25)
				0.25			0.22
Never	1718	Ref.			1718	Ref.	
Snus only up to 18w	126	0.19	(-0.00, 0.37)		126	0.19	(0.01, 0.40)
Snus only up to 34w	10	0.19	(-0.45, 0.84)		10	0.002	(-0.61, 0.61)
Smoke/dual	88	0.04	(-0.19, 0.26)		88	0.04	(-0.17, 0.25)

\*The results of the multivariable analyses restricted by the same study population as in the sensitivity analyses without adjusting for gestational weight gain, were similar in both populations (data not shown). Covariates used in multivariable analyses: 1=Parity, 2=gestational age at birth, 3=fetal sex, 4=pre-pregnancy body mass index, 5=maternal age, 6=living area, 7=gestational weight gain up to 18 weeks of pregnancy.

No.=number, B=beta coefficient, CI=confidence interval, Ref.=reference value, w=week.

**Table S5. Linear regression analyses: Effect of tobacco exposure during pregnancy on proportional size measures (ratio).** The reference group ‘Never’ includes all women who did not report use of tobacco or nicotine during pregnancy. The ‘Smoke/dual’ group includes dual smokers and snus users during pregnancy of who most quit before 6 weeks of pregnancy.

Tobacco exposure during pregnancy	No.	B	95% CI	P-value	No.	B	95% CI	P-value
	<b>Abdominal circumference/head circumference</b>							
	<b>Univariable</b>				<b>Multivariable (1-4)</b>			
				0.46				0.36
Never	1724	Ref.			1724	Ref.		
Snus only	139	-0.005	(-0.02, 0.00)		139	-0.005	(-0.02, 0.01)	
Smoke/dual	90	-0.004	(-0.02, 0.01)		90	-0.007	(-0.02, 0.01)	
				0.60				0.48
Never	1724	Ref.			1661	Ref.		
Snus only up to 18w	129	-0.005	(-0.02, 0.01)		126	-0.004	(-0.01, 0.01)	
Snus only up to 34w	10	-0.014	(-0.05, 0.02)		10	-0.016	(-0.05, 0.02)	
Smoke/dual	90	-0.004	(-0.02, 0.01)		87	-0.007	(-0.02, 0.01)	
<b>Thoracic circumference/Abdominal circumference</b>								
	<b>Univariable</b>				<b>Multivariable (2)</b>			
				0.10				0.09
Never	1889	Ref.			1889	Ref.		
Snus	140	0.003	(-0.01, 0.01)		140	0.003	(-0.01, 0.01)	
Smoke/dual	90	0.01	(0.00, 0.02)		90	0.01	(0.00, 0.02)	
				0.12				0.10
Never	1889	Ref.			1889	Ref.		
Snus only up to 18w	129	0.004	(-0.00, 0.01)		129	0.004	(-0.01, 0.01)	
Snus only up to 34w	11	-0.01	(-0.04, 0.02)		11	-0.01	(-0.04, 0.02)	
Smoke/dual	90	0.01	(0.00, 0.02)		90	0.01	(0.00, 0.02)	
<b>Thoracic circumference/Head circumference</b>								
	<b>Univariable</b>				<b>Multivariable (1-4)</b>			
				0.72				0.68
Never	1695	Ref.			1695	Ref.		
Snus	139	-0.002	(-0.01, 0.01)		139	-0.003	(-0.01, 0.01)	
Smoke/dual	88	0.003	(-0.01, 0.01)		88	0.003	(-0.01, 0.01)	
				0.55				0.41
Never	1695	Ref.			1695	Ref.		
Snus only up to 18w	129	-0.001	(-0.01, 0.01)		129	-0.001	(-0.01, 0.01)	
Snus only up to 34w	10	-0.02	(-0.05, 0.01)		10	-0.03	(-0.06, 0.01)	
Smoke/dual	88	0.003	(-0.01, 0.01)		88	0.003	(-0.01, 0.01)	

Birth weight/Placenta weight							
Univariable				Multivariable (1-4)			
				0.65			0.46
Never	1368	Ref.			1340	Ref.	
Snus	126	-0.09	(-0.34, 0.16)		126	-0.12	(-0.37, 0.12)
Smoke/dual	64	0.10	(-0.24, 0.43)		64	0.12	(-0.21, 0.46)
				0.83			0.67
Never	1368	Ref.			1368	Ref.	
Snus only up to 18w	116	-0.10	(-0.35, 0.16)		116	-0.12	(-0.38, 0.13)
Snus only up to 34w	10	-0.02	(-0.86, 0.82)		10	-0.13	(-0.97, 0.70)
Smoke/dual	64	0.10	(-0.24, 0.43)		64	0.12	(-0.22, 0.46)

Covariates used in multivariable analyses: 1=Parity, 2=gestational age at birth, 3=fetal sex, 4=maternal age.

No.number, B=beta coefficient, CI=confidence interval, Ref.=reference value

**Figure S1 Study population.**

