

Maternal Use of Swedish Snuff (Snus) and Risk of Stillbirth

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Background: Swedish snuff has been discussed internationally as a safer alternative to tobacco smoking. International cigarette manufacturers are promoting new snuff products, and the use of Swedish snuff is increasing, especially among women of child-bearing age. The effect of Swedish snuff on pregnancy complications is unknown.

Methods: In this population-based cohort study, we estimated the risk of stillbirth in snuff users ($n = 7629$), light smokers ($1-9$ cigarettes/day; $n = 41,488$), and heavy smokers (≥ 10 cigarettes/day; $n = 17,014$), using nontobacco users ($n = 504,531$) as reference.

Results: Compared with nontobacco users, snuff users had an increased risk of stillbirth (adjusted odds ratio = 1.6 [95% confidence interval = 1.1–2.3]); the risk was higher for preterm (<37 weeks) stillbirth (2.1 [1.3–3.4]). For light smokers, the adjusted odds ratio of stillbirth was 1.4 (1.2–1.7) and the corresponding risk for heavy smokers was 2.4 (2.0–3.0). When we excluded women with preeclampsia or antenatal bleeding and infants who were small for gestational age, the smoking-related risks of stillbirth was markedly attenuated; the elevated risk for snuff users remained the same level.

Conclusions: Use of Swedish snuff during pregnancy was associated with a higher risk of stillbirth. The mechanism behind this increased risk seems to differ from the underlying mechanism in smokers. Swedish snuff does not appear to be a safe alternative to cigarette smoking during pregnancy.

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The use of smokeless tobacco has increased both in Sweden and globally, and especially among women of child-bearing age.^{1,2} The use of Swedish smokeless tobacco (called Swedish snuff or snus) may continue to increase for several

reasons. First, Swedish snuff has been discussed as a means of reducing harm among tobacco-addicted persons, as snus seems to be less harmful than cigarette smoking with regard to risks for cardiovascular disease and cancer.³ Second, smoke-free public places, which are rapidly becoming the norm, reduce smoking rates⁴ but not necessarily tobacco use, as smokeless tobacco may be chosen by some people as an alternative to remain on nicotine. Third, international cigarette manufacturers are now promoting new snuff products to attract youth and women, who have traditionally not used smokeless products.

Stillbirth is a relatively rare adverse pregnancy outcome in high-income countries such as Sweden, but is probably one of the most tragic events that expectant parents can experience.^{5,6} Cigarette smoking is associated with increased stillbirth risk, especially early stillbirth, and both nicotine and products of combustion (eg, carbon monoxide) have been proposed to increase risk.^{7–12} Swedish snuff delivers quantities of nicotine comparable to cigarette smoking but without exposure to products of combustion.^{13,14} The effect of Swedish snuff on stillbirth risk is unknown.

Given the increased global use of Swedish snuff as a nonsmoking nicotine alternative, we investigated the association between Swedish snuff and risk of stillbirth using a large population-based cohort. Furthermore, we compared the effects of Swedish snuff and cigarette smoking on the risk of stillbirth to explore whether the increased risk of stillbirth with cigarette smoking is due to nicotine or to tobacco combustion products.

METHODS

Study Population

Information from the Swedish Medical Birth Register was used to define the study population. Women born in the Nordic countries (Sweden, Norway, Denmark, Finland, or Iceland) who delivered a singleton infant in Sweden at 28 weeks' gestation or more during the years 1999–2006 were included ($n = 610,879$). The Birth Register contains data on more than 99% of all births in Sweden, including demographic data, information on reproductive history and complications during pregnancy, delivery, and the neonatal period.¹⁵ Using each person's unique national registration number, the Birth Register can be linked with other Swedish data sources.

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Stillbirths are registered in the Birth Register. During these years, stillbirth was defined as fetal death at 28 weeks of gestation or later. In the Birth Register, information about maternal cigarette smoking has been recorded since 1983 and snuff use since 1999. This information is collected by midwives at the woman's first antenatal visit, which occurs before the 15th week of gestation in more than 95% of pregnancies.¹⁶ Tobacco habits are categorized into nontobacco users, snuff users, light smokers (1–9 cigarettes per day), and heavy smokers (at least 10 cigarettes per day). In the study population, 7629 women were reported as snuff users; 41,488 women as light smokers; 17,014 women as heavy smokers; and 483 women as both daily snuff users and daily smokers. Information about current tobacco use was missing in 39,734 (7%) women.

Information about parity (categorized as 0, 1–2, or ≥ 3), body mass index (BMI; categorized as underweight [<20 kg/m²], normal weight [20–24.9 kg/m²], overweight [25–29.9 kg/m²], or obese [≥ 30 kg/m²]), and pre-existing diagnosis of diabetes mellitus or chronic hypertension was also collected at the first antenatal visit. Maternal age was recorded when the woman was discharged from the delivery hospital. The years of formal education (≤ 9 , 10–12, 13–14, or ≥ 15) and mother's country of birth were obtained by linking the Birth Register to the Education Register and the Register of Total Population, respectively, both held by Statistics Sweden.

Complications during pregnancy and delivery were classified according to the International Classification of Diseases, 10th version (ICD-10) as noted by the responsible doctor at discharge from hospital. Diabetes mellitus was categorized into pregestational insulin-dependent diabetes (identified at the first antenatal visit or by the ICD-10 codes O240 and O243 reported at discharge) or gestational diabetes (ICD-10 code O244). Hypertensive disease was categorized into chronic hypertension (identified at the first antenatal visit or by ICD-10 codes O10 and O11); severe preeclampsia (ICD-10 codes O141 and O15); mild preeclampsia (ICD-10 codes O140 and O149); or gestational hypertension (ICD-10 code O13). Antenatal bleeding was defined as placenta praevia, placental abruption, or other reasons for antenatal bleeding (ICD-10 codes O44, O45, and O46). Small-for-gestational-age (SGA) was defined as a birth weight of 2 or more standard deviations below the mean birth weight for gestational age according to sex-specific Swedish fetal growth curves.¹⁷ In Sweden, gestational age is assessed by ultrasound scans in 95% of women, usually around the 17th week of gestation.¹⁸ If no early-second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery. Preterm birth was defined as a delivery before 37 gestational weeks and term birth as a delivery at 37 gestational weeks or later. The study was approved by one of the Regional Ethical Review Boards in Stockholm, Sweden. The board did not require the women to provide informed consent.

Statistical Analysis

We calculated risks of stillbirth for snuff users, light smokers, heavy smokers and women who daily used both snuff and cigarettes, using nontobacco users as reference group. Women with missing information on tobacco habits were excluded from analyses. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using SAS PROC GENMOD in Statistical Analysis Software version 9.1 (SAS Institute Inc, Cary, NC). When calculating adjusted risks of stillbirth, we excluded women who reported daily use of both snuff and cigarettes due to small numbers. Confounders were maternal age at delivery, early pregnancy BMI, parity, years of mother's formal education, chronic hypertension, and pregestational diabetes. We also wanted to investigate whether stillbirth risk in tobacco users was mediated by previously-reported smoking-related pregnancy complications and outcomes. We therefore calculated snuff and cigarette use and stillbirth risk after excluding women with preeclampsia, antenatal bleeding, and delivery of an SGA infant. We also constructed a plot of stillbirth risk by gestational age, stratified by tobacco habits. The gestational-age-specific risk was defined as the number of stillbirths during a time interval (week 28 and then in 2-week intervals) divided by the total number of fetuses undelivered at the beginning of the interval. The proportion was multiplied by 10,000 to provide a gestational-age-specific stillbirth rate per 10,000 undelivered fetuses.

RESULTS

Compared with nontobacco users, women who used snuff or smoked cigarettes during pregnancy were more often younger than 20 years (Table 1). Light smokers were less likely to be at least 35 years, whereas snuff users and heavy smokers were more likely to be at least 35 years. Furthermore, snuff users and smokers, especially heavy smokers, were more often multiparous compared with nontobacco users. More than 50% of nontobacco users had normal weight; the corresponding percents were 46% for snuff users, 42% for light smokers, and 38% for heavy smokers. Fifty percent of nontobacco users, 34% of snuff-users, 13% of light, and 9% of heavy smokers had 13 years or more of formal education (Table 1).

Among 610,879 births, there were 1926 stillbirths (3.2 per 1000 births). Compared with nontobacco users, snuff users, and smokers had higher risks of stillbirth; the risk increased with amount of cigarette smoked (Table 2). There was a U-shaped association between maternal age, parity, and stillbirth risk. Risk of stillbirth increased with increasing BMI and decreased with increasing length of maternal formal education. Maternal chronic diseases (pregestational diabetes and hypertension) and some pregnancy complications (severe preeclampsia, antenatal bleeding, and SGA at birth) were associated with substantially-increased risks of stillbirth. In contrast, gestational diabetes, gestational hypertension, and mild preeclampsia were not associated with increased risk (Table 2).

TABLE 1. Maternal Characteristics and Pregnancy Complications by Tobacco Use; 610,879 Single Births in Sweden, 1999–2006

	No Tobacco (n = 504,531) %	Snuff (n = 7629) %	No. Cigarettes/Day		Both Snuff and Cigarettes (n = 483) %
			1–9 (n = 41,488) %	≥10 (n = 17,014) %	
Maternal characteristics					
Maternal age (years)					
≤19	1.1	1.9	6.4	3.6	4.1
20–24	10.3	13.2	24.7	17.9	20.7
25–29	32.7	29.6	29.4	27.1	23.8
30–34	37.5	24.0	23.9	28.5	28.6
≥35	18.4	21.4	15.5	22.9	27.8
Parity					
0	45.6	42.9	46.8	30.4	43.9
1–2	50.2	49.8	45.2	51.2	46.2
≥3	4.2	7.3	8.0	18.5	9.9
BMI (kg/m ²)					
≤19	7.9	7.4	9.5	8.2	9.1
20–24	50.4	45.7	41.7	38.3	43.3
25–29	21.9	24.2	23.8	24.2	21.3
≥30	9.2	11.0	13.3	16.7	15.5
Missing	10.7	11.6	11.8	12.6	10.8
Education (years)					
≤9	5.1	10.2	24.8	31.8	23.4
10–12	45.0	55.7	61.6	58.8	59.4
13–14	16.1	12.9	7.0	5.3	8.5
≥15	33.6	21.0	6.0	3.5	8.7
Missing	0.1	0.1	0.6	0.6	0.0
Pregnancy complications					
Diabetes mellitus					
No diabetes	98.7	98.7	98.5	98.0	98.6
Pregestational diabetes	0.7	0.7	0.8	1.0	1.0
Gestational diabetes	0.6	0.5	0.7	1.0	0.4
Hypertension					
No hypertension	95.4	95.0	96.6	97.1	95.0
Chronic hypertension	0.6	0.7	0.5	0.6	0.6
Severe preeclampsia	0.9	1.1	0.6	0.5	1.0
Mild preeclampsia	2.1	2.4	1.7	1.3	1.9
Gestational hypertension	0.9	0.7	0.6	0.5	1.4
Antenatal bleeding					
Yes	1.0	1.2	1.4	2.0	1.0
No	99.0	98.8	98.6	98.0	99.0
Small for gestational age (SGA)					
Yes	1.7	2.0	4.0	4.9	4.8
No	97.8	97.5	95.4	94.4	94.8
Missing	0.5	0.5	0.6	0.6	0.4

Table 3 shows the associations of maternal snuff use and smoking on pregnancy complications. Compared with nontobacco users, snuff users did not have higher risks of preeclampsia, antenatal bleeding, or giving birth to a SGA infant. Smokers had lower risks of preeclampsia and higher risks of antenatal bleeding and SGA, with evidence of dose-response patterns.

In the adjusted analysis, snuff users had 60% higher risk for stillbirth than nontobacco users (Table 4). The adjusted risk of stillbirth among light smokers was slightly lower than among snuff users, whereas heavy smokers had a more-than-doubled risk compared with nontobacco users. To investigate if these risks were mediated by pregnancy complications, we excluded

TABLE 2. Association of Maternal Characteristics and Pregnancy Complications With Stillbirth. Single Births in Sweden, 1999–2006

	No. Births	No. Stillbirths	Rate (1/1000)	OR (95% CI)
Maternal characteristics				
Tobacco use				
None ^a	504,531	1386	2.7	1.00
Snuff	7629	40	5.2	1.91 (1.40–2.62)
Cigarettes (no./day)				
1–9	41,488	172	4.1	1.51 (1.29–1.77)
≥10	17,014	120	7.1	2.58 (2.14–3.11)
Both snuff and cigarettes	483	4	8.3	3.03 (1.13–8.12)
Missing	39,734	204	5.1	
Maternal age (years)				
≤19	9740	41	4.2	1.49 (1.06–2.10)
20–24	70,128	217	3.1	1.15 (0.97–1.35)
25–29 ^a	194,990	526	2.7	1.00
30–34	222,038	688	3.1	1.17 (1.04–1.32)
≥35	113,983	454	4.0	1.51 (1.32–1.72)
Parity				
0	276,243	1290	4.7	2.48 (2.24–2.76)
1–2 ^a	304,404	552	1.8	1.00
≥3	30,232	84	2.8	1.54 (1.22–1.96)
BMI (kg/m ²)				
≤19.9	46,677	105	2.2	0.94 (0.76–1.16)
20–24.9 ^a	287,723	681	2.4	1.00
25–29.9	129,007	463	3.6	1.50 (1.33–1.69)
≥30	56,970	334	5.9	2.45 (2.15–2.80)
Missing	90,502	343	3.4	
Education (years)				
≤9	45,150	187	4.1	1.55 (1.27–1.89)
10–12	283,402	1019	3.6	1.34 (1.16–1.56)
13–14 ^a	92,310	248	2.7	1.00
≥15	188,841	467	2.5	0.92 (0.78–1.09)
Missing	1176	5	4.3	
Pregnancy complications				
Diabetes mellitus				
No diabetes ^a	602,673	1872	3.1	1.00
Pregestational diabetes	3994	39	9.8	3.33 (2.38–4.66)
Gestational diabetes	4212	15	3.6	1.20 (0.71–2.03)
Hypertension				
No hypertension ^a	583,503	1817	3.1	1.00
Chronic hypertension	3804	34	8.9	2.92 (2.05–4.18)
Severe preeclampsia	5567	38	6.8	2.10 (1.48–3.00)
Mild preeclampsia	12,421	25	2.0	0.61 (0.39–0.93)
Gestational hypertension	5584	12	2.1	0.78 (0.44–1.38)
Antenatal bleeding				
Yes	6547	178	27.2	10.1 (8.60–11.9)
No ^a	604,332	1748	2.9	1.00
Small for gestational age (SGA)				
Yes	11,930	434	36.4	15.6 (13.9–17.5)
No ^a	595,954	1434	2.4	1.00
Missing	2995	58	19.4	
Total births	610,879	1926	3.15	

^aReference category.

TABLE 3. Association of Maternal Tobacco Use With Preeclampsia, Antenatal Bleeding, and Giving Birth to SGA Infant

Tobacco Use	Preeclampsia		Antenatal Bleeding ^a		Small for Gestational Age	
	No. Cases (%)	Adjusted ^b OR (95% CI)	No. Cases (%)	Adjusted ^b OR (95% CI)	No. Cases (%)	Adjusted ^b OR (95% CI)
None ^c	15,709 (3.1)	1.00	4971 (1.0)	1.00	8430 (1.7)	1.00
Snuff user	272 (3.6)	1.12 (0.98–1.28)	90 (1.2)	1.15 (0.92–1.44)	150 (2.0)	1.17 (0.98–1.39)
Cigarettes (no./day)						
1–9	994 (2.4)	0.66 (0.61–0.71)	583 (1.4)	1.51 (1.37–1.66)	1653 (4.0)	2.34 (2.21–2.49)
≥10	310 (1.8)	0.52 (0.46–0.60)	338 (2.0)	1.88 (1.65–2.13)	833 (4.9)	3.20 (2.94–3.48)

^aPlacenta praevia, placental abruption, or other reasons for antenatal bleeding.^bAdjusted for maternal age, BMI, parity, years of education, chronic hypertension, and pre-gestational diabetes.^cReference category.**TABLE 4.** Association of Maternal Tobacco Use With Stillbirth

Tobacco Use	Stillbirth			Restricted Model of Stillbirth ^a		
	No. Cases	Rate (1/1000)	Adjusted ^b OR (95% CI)	No. Cases	Rate (1/1000)	Adjusted ^b OR (95% CI)
None ^c	1386	2.7	1.00	985	2.1	1.00
Snuff	40	5.2	1.60 (1.13–2.29)	29	4.1	1.57 (1.03–2.41)
Cigarettes (no./day)						
1–9	172	4.1	1.40 (1.17–1.67)	99	2.6	1.15 (0.91–1.45)
≥10	120	7.1	2.42 (1.96–2.99)	58	3.7	1.85 (1.39–2.46)

^aAfter exclusion of women with preeclampsia, antenatal bleeding, and infants born small for gestational age (SGA).^bAdjusted for maternal age, BMI, parity, years of education, chronic hypertension, and pre-gestational diabetes.^cReference category.

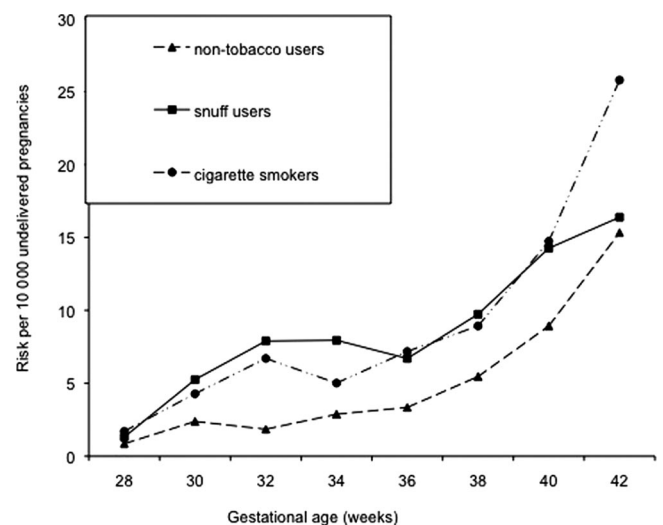
women with diagnosis of preeclampsia, antenatal bleeding, and those giving birth to an SGA infant. The odds ratio for stillbirth in snuff users was unchanged, whereas the odds ratios decreased among smokers (Table 4).

Compared with women who did not use tobacco, snuff users had more than twice the odds of preterm stillbirth (<37 weeks; adjusted OR = 2.1 [95% CI = 1.3–3.4]), whereas the odds ratio for stillbirth with snuff use in term pregnancy (≥37 weeks) was only slightly increased (1.3 [0.76–2.1]). Cigarette smoking also had a stronger association with preterm stillbirths (1.7 [1.3–2.2] for light smokers and 3.0 [2.2–4.0] for heavy smokers), than with term stillbirth (1.2 [0.95–1.5] for light smokers and 2.1 [1.5–2.8] for heavy smokers).

In the Figure, the stillbirth rate per 10,000 undelivered pregnancies is stratified by maternal tobacco habits and plotted by gestational age. In all strata the rate of stillbirth increased with gestational length. Snuff users and cigarette smokers had higher stillbirth rates than nontobacco users, especially in the preterm period.

DISCUSSION

In this large population-based study, Swedish snuff users had a higher risk of stillbirth than nontobacco users. We confirmed earlier findings of a dose-dependent increased stillbirth risk in cigarette smokers. Both snuff users and

**FIGURE.** Stillbirth rate per 10,000 undelivered pregnancies by gestational age, stratified by maternal tobacco use.

smokers had stronger associations with preterm stillbirths than term stillbirths.

The increased risk of stillbirth in cigarette smokers has been explained to a large extent by complications of antenatal bleeding or fetal growth restriction.^{10,19} When we excluded

women with pregnancy complications (preeclampsia, antenatal bleedings, and infants born SGA), we found that the increased risk for stillbirth was greatly reduced for smokers but not for snuff users. This suggests different mechanisms for the increased stillbirth risk in snuff users and smokers. Stillbirth risk in cigarette smokers is strongly associated with fetal growth restriction (measured as delivery of a SGA infant).^{6,10,20} Cigarette smoke includes several components, eg, nicotine,²¹ carbon monoxide,²² and cadmium,²² that might affect fetal growth. The shared exposure in cigarette smoke and Swedish snuff is nicotine.^{1,13,14} In addition to causing a reduction in uterine blood flow,²³ nicotine exposure during fetal developmental can produce cardiac and brain-stem-receptor imbalances in animal studies.^{24,25} Snuff and cigarette smoke deliver comparable nicotine quantities, but snuff has slower nicotine absorption and lack the high blood-concentration peaks associated with cigarette smoke.^{13,14} Nicotine readily gains access to the fetal compartment via the placenta, with fetal concentrations generally 15% higher than maternal levels.²³ The different patterns of nicotine concentrations in maternal blood in snuff users and cigarette smokers might have different effects on the developing fetus and placenta.

There are 2 main forms of smokeless tobacco: snuff and chewing tobacco. Smokeless tobacco is most prevalent among women in low-income countries, mainly in the form of chewing tobacco and sometimes including ingredients other than tobacco, eg, areca nuts.²⁶ A previous report has described stillbirth risk among a cohort in India where women used chewing tobacco (mainly mishri) during pregnancy.²⁶ The study included 201 smokeless tobacco users and found that smokeless tobacco users had a 2.5 times higher risk of stillbirth than nontobacco users. There are differences in contents between mishri and Swedish snuff, and also major sociodemographic and cultural differences between the populations. However, the results from the Indian study are in general agreement with our findings.

The increased stillbirth risk among light smokers in our study is similar to findings of earlier studies,^{12,27} while the 2-fold increased stillbirth risk in heavy smokers was larger than expected. In studies from the 1980s and 1990s, ORs of 1.6–1.8 were reported for stillbirth in heavy smokers compared with nontobacco users.^{9,12,27} One reason for the higher risk in our study may be residual social confounding. Along with a decreasing proportion of smokers among pregnant women, relative socioeconomic status among pregnant smokers has decreased during the last 20 years in Sweden.²⁸ Low socioeconomic status is associated with increased risk of stillbirth even after adjustment for maternal age, BMI, smoking, and occupation.²⁹ In addition, heavy smokers were defined as women smoking at least 10 cigarettes at the first antenatal visit. Heavy smokers today may smoke more and be less likely to quit later during pregnancy.

Among high-income countries, Sweden has the highest per capita consumption of smokeless tobacco. An oral, moist snuff called snus is the predominant form used. Swedish snuff contains lower levels of some harmful substances (eg, nitrosamines) than many of the smokeless tobacco brands available in United States and low-income countries.¹⁴ Epidemiologic studies suggest that overall health risks associated with Swedish snuff are much lower than those of smoking.^{14,30} Swedish snuff has been suggested as a less harmful form of tobacco for persons addicted to tobacco, and is now being introduced into the United States.³ Promoting snuff use may reduce cigarette smoking, but it may also lead to recruitment of new tobacco users.³¹ The findings of an association between snuff use and stillbirth raises serious questions about promoting snuff use as alternative nicotine source during pregnancy.

A major strength of the present study is the nationwide population-based design, with information on current tobacco use at the first antenatal visit for 94% of pregnant women. We adjusted for a number of possible confounders and restricted to a relatively homogeneous population of women born in the Nordic countries. Moreover, antenatal and obstetric care is free of charge, management routines are standardized and more than 99% of births are delivered in public hospitals. Such factors should minimize the potential for confounding by unmeasured socio-demographic factors or differences in management. Further strengths of the study are that information about current tobacco use was collected by interviews in early pregnancy, before the occurrence of the outcome, which precludes recall bias. Self-reported information on smoking during pregnancy has been validated in Sweden,³² but we lack validation studies with respect to snuff use. We also lack information on potential confounders such as consumption of alcohol and other drugs, domestic violence, differences in diet and exposure to infections. Another limitation is that information on tobacco exposure was obtained at 1 time point in early pregnancy. Some women may have stopped using tobacco later in pregnancy, whereas others who were not using tobacco products at the time of interview may later have resumed snuff use or cigarette smoking. About 10% of the women who have stopped smoking in early pregnancy are estimated to resume later in pregnancy.³²

In conclusion, the use of Swedish snuff was associated with a marked increase in the risk of stillbirth. The biologic mechanism behind the increased risk of stillbirth may differ between snuff users and cigarette smokers.

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