



## **APPENDIX AVAILABLE ON REQUEST**

### **Research Report 139**

#### **Effects of Long-Term Exposure to Traffic-Related Air Pollution on Respiratory and Cardiovascular Mortality in the Netherlands: The NLCS-AIR Study**

**Bert Brunekreef et al.**

#### **Appendix F. Full Cohort and Case-Cohort Analyses**

Note: Appendices Available on the Web appear in a different order than in the original Investigators' Report. HEI has not changed these documents. Appendices were relettered as follows:

Appendix C was originally Appendix 1  
Appendix D was originally Appendix 2  
Appendix E was originally Appendix 3  
Appendix F was originally Appendix 4

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This document was reviewed by the HEI Health Review Committee but did not undergo the HEI scientific editing and production process.



## Appendix 4 Full cohort and case-cohort analyses

This appendix contains the results of analyses that compared the effect estimates for air pollution using analyses in the case-cohort sample and the full cohort.

Complete confounder information is only available for the subcohort and for subjects who died or developed cancer during follow-up. As a result, analyses adjusted for all available confounders from the questionnaire are only possible using the case-cohort approach. These potential confounders were chosen a priori. For the full cohort analyses only a limited number of confounders are available (age, gender, smoking status and four area level socio-economic status variables).

Table 1 presents the association between cause-specific mortality and the Black Smoke background concentration for the period 1987-1996 and traffic intensity on the nearest road, using the case-cohort and full cohort approach and three different confounder models. Table 1 illustrates several methodological issues that are critical in the interpretation of our findings. The observed patterns were reproduced when we looked at other pollutants and other traffic variables in the analysis.

In the unadjusted models, we found elevated relative risks for the *background* concentration of BS both in the case-cohort and the full cohort analyses for all causes of death. Confidence intervals were substantially smaller for the full cohort analyses compared to the case-cohort analyses, supporting the inclusion of full cohort analyses compared to the originally planned case-cohort analyses. The role of sampling from the full cohort is further analyzed below. After adjusting for all available confounders, RR's for background concentration were reduced in the full cohort and reduced to essentially unity in the case-cohort analyses (except respiratory mortality). In the case cohort analyses, the occurrence of missing values on one or more potential confounders led to a strong reduction of the number of subjects available for analysis, to about 60% of the original number. An unadjusted analysis in this remaining population, showed RR's that were substantially smaller than the unadjusted RR's in the complete population. In fact, the largest part of the difference between adjusted and unadjusted RR's in the case-cohort analysis is due to this selection effect and not to confounding. We conducted a similar analysis in the full cohort with the more limited set of confounders available for analysis, and found less evidence of such a selection effect.

Table 1. Association between background Black Smoke concentration (period 1987-1996) and traffic intensity on nearest road and cause-specific mortality in case-cohort and full cohort sample, using different confounder models .\*

<b>Mortality</b>	<b>Confounder model</b>	<b>Population</b>	<b>Case-cohort</b>	<b>n</b>	<b>Full cohort</b>	<b>N</b>
<b>Natural cause</b>						
Black smoke	Unadjusted	All	1.15 (0.97 – 1.15)	21,453	1.14 (1.07 – 1.22)	117,499
Traffic intensity			0.99 (0.91 – 1.08)		1.04 (1.00 – 1.08)	
Black smoke	Adjusted	Complete confounder data	0.99 (0.75 – 1.31)	12,720	1.09 (1.00 – 1.19)	105,296
Traffic intensity			0.99 (0.88 – 1.11)		1.03 (1.00 – 1.08)	
Black smoke	Unadjusted	Complete confounder data	1.03 (0.83 – 1.28)	12,720	1.15 (1.07 – 1.24)	105,296
Traffic intensity			1.00 (0.90 – 1.12)		1.04 (1.01 – 1.09)	
Black smoke	Adjusted full cohort confounders	Complete confounder data	0.99 (0.76 – 1.19)	12,720	-	-
Traffic intensity			0.98 (0.88 – 1.09)		-	-
<b>Cardiopulmonary</b>						
Black smoke	Unadjusted	All	1.17 (0.97 – 1.42)	11,732	1.17 (1.05 – 1.30)	117,499
Traffic intensity			1.01 (0.92 – 1.11)		1.07 (1.02 – 1.13)	
Black smoke	Adjusted	Complete confounder data	1.06 (0.76 – 1.48)	7,059	1.12 (0.98 – 1.28)	105,296
Traffic intensity			1.02 (0.90 – 1.16)		1.06 (1.00 – 1.12)	
Black smoke	Unadjusted	Complete confounder data	1.08 (0.84 – 1.40)	7,059	1.18 (1.06 – 1.33)	105,296
Traffic intensity			1.02 (0.90 – 1.16)		1.07 (1.01 – 1.13)	
Black smoke	Adjusted full cohort confounders	Complete confounder data	1.06 (0.77 – 1.44)	7,059	-	-
Traffic intensity			0.99 (0.88 – 1.12)		-	-
<b>Cardiovascular</b>						
Black smoke	Unadjusted	All	1.14 (0.94 – 1.38)	10,761	1.14 (1.02 – 1.28)	117,499
Traffic intensity			1.00 (0.91 – 1.10)		1.06 (1.00 – 1.13)	
Black smoke	Adjusted	Complete confounder data	1.00 (0.72 – 1.40)	6,510	1.11 (0.96 – 1.28)	105,296
Traffic intensity			1.03 (0.90 – 1.17)		1.05 (0.99 – 1.12)	
Black smoke	Unadjusted	Complete confounder data	1.05 (0.81 – 1.36)	6,510	1.16 (1.03 – 1.31)	105,296
Traffic intensity			1.02 (0.91 – 1.16)		1.06 (1.00 – 1.13)	
Black smoke	Adjusted full cohort confounders	Complete confounder data	1.01 (0.74 – 1.39)	6,510	-	-
Traffic intensity			1.00 (0.88 – 1.13)		-	-
<b>Respiratory</b>						
Black smoke	Unadjusted	All	1.42 (1.01 – 2.00)	5,846	1.41 (1.06 – 1.88)	117,499
Traffic intensity			1.04 (0.91 – 1.19)		1.13 (0.99 – 1.27)	
Black smoke	Adjusted	Complete confounder data	1.52 (0.80 – 2.88)	3,607	1.22 (0.86 – 1.74)	105,296
Traffic intensity			0.94 (0.71 – 1.25)		1.10 (0.95 – 1.26)	
Black smoke	Unadjusted	Complete confounder data	1.31 (0.82 – 2.10)	3,607	1.34 (0.99 – 1.82)	105,296
Traffic intensity			1.01 (0.80 – 1.27)		1.11 (0.97 – 1.27)	
Black smoke	Adjusted full cohort confounders	Complete confounder data	1.33 (0.77 – 2.31)	3,607	-	-
Traffic intensity			0.97 (0.77 – 1.21)		-	-

<b>Mortality</b>	<b>Confounder model</b>	<b>Population</b>	<b>Case-cohort</b>	<b>n</b>	<b>Full cohort</b>	<b>N</b>
<b>Lung cancer</b>						
Black smoke	Unadjusted	All	1.17 (0.89 – 1.53)	6,692	1.15 (0.94 – 1.42)	117,499
Traffic intensity			1.00 (0.89 – 1.13)		1.06 (0.95 – 1.18)	
Black smoke	Adjusted	Complete confounder data	1.02 (0.61 – 1.71)	4,075	1.01 (0.78 – 1.32)	105,296
Traffic intensity			1.03 (0.87 – 1.22)		1.07 (0.96 – 1.19)	
Black smoke	Unadjusted	Complete confounder data	1.03 (0.71 – 1.48)	4,075	1.09 (0.87 – 1.37)	105,296
Traffic intensity			1.07 (0.92 – 1.24)		1.09 (0.97 – 1.21)	
Black smoke	Adjusted full cohort confounders	Complete confounder data	0.93 (0.59 – 1.48)	4,075	-	-
Traffic intensity			1.01 (0.86 – 1.17)		-	-
<b>Non-cardiopulmonary, non lung cancer</b>						
Black smoke	Unadjusted	All	1.12 (0.94 – 1.33)	13,096	1.11 (1.01 – 1.22)	117,499
Traffic intensity			0.97 (0.89 – 1.05)		1.00 (0.95 – 1.06)	
Black smoke	Adjusted	Complete confounder data	0.95 (0.71 – 1.26)	7,883	1.09 (0.96 – 1.23)	105,296
Traffic intensity			0.93 (0.82 – 1.06)		1.00 (0.94 – 1.06)	
Black smoke	Unadjusted	Complete confounder data	0.98 (0.78 – 1.23)	7,883	1.13 (1.02 – 1.26)	105,296
Traffic intensity			0.96 (0.85 – 1.08)		1.00 (0.95 – 1.06)	
Black smoke	Adjusted full cohort confounders	Complete confounder data	0.96 (0.73 – 1.25)	7,883	-	-
Traffic intensity			0.94 (0.84 – 1.06)		-	-

\* Confounder models: *unadjusted*: adjusted for age and gender; *adjusted*: adjusted for all available potential confounders; *unadjusted with complete data*: adjusted for age and gender but only including the subjects that had complete information for all possible confounders included in the adjusted model and *adjusted with full cohort confounder model with complete data*: adjusted for confounders of full cohort confounder model but only including the subjects that had complete information for all possible confounders included in the adjusted model.

Confounders in adjusted analysis:

*Case-cohort confounder model*: age, gender, BMI, active smoking, passive smoking, education, occupational exposure, marital status, alcohol use, vegetable intake, fruit intake, energy intake, fatty acids intake, folic acid intake, fish consumption, percentage persons with low and high income in a neighborhood, and percentage persons with low and high income in a COROP area.

*Full cohort confounder model*: age, gender, active smoking, percentage persons with low and percentage persons with high income in a neighborhood, and percentage persons with low and high income in a COROP area.

RRs were calculated for concentration changes from the 5<sup>th</sup> to the 95<sup>th</sup> percentile: 10 µg/m<sup>3</sup> for BS background/overall estimate and 10,000 mvh/24 h for traffic intensity on the nearest road

Table 1 further illustrates that in case cohort analyses there was little difference between the effect estimates adjusted for the limited set of full cohort confounders and the fully adjusted effect estimates, suggesting that inclusion of the full set of potential confounders in fact made little difference in the case cohort analysis. The biggest difference was for respiratory mortality where the fully adjusted effect estimate in the case cohort analysis was higher than the unadjusted or partially adjusted one. This suggests that the pattern of adjustment would be the same in the full cohort analysis if data on all confounders had been available for analysis. However, as these analyses were only possible in the case-cohort sample, we cannot exclude some residual confounding in the full cohort analyses.

As a next step, we investigated in the case cohort analysis whether it was possible to add additional covariates to the limited full cohort confounder model with smaller losses in the number of subjects and less selection. The “start”-confounder model was the model that is used in the full cohort analyses (age, gender, active smoking, neighborhood SES and COROP area SES). To this start-model we added variables separately that were marginally associated with total mortality ( $p$ -value  $< 0.2$ ) in the model with all possible confounders included. We then added all variables for which no selection effect was apparent. The detailed results are shown in Table 2. The bottom line is that with the exception of diet, none of the covariates was particularly responsible for the selection effect. When we introduced all covariates with the exception of diet in the analysis, we found no selection effect for cardio-pulmonary and respiratory mortality, but for the other causes the selection effect again occurred. This suggests that we cannot omit just one or two covariates from the fully adjusted analyses in order to produce a result in which missing values do not produce a difference in the unadjusted effect estimates between the full group and the restricted group that has all covariate information. For cardio-pulmonary mortality, there were very small differences between the adjusted RR's in the case-cohort analyses between the limited confounder model and the complete (excl diet) confounder model and the full cohort. For respiratory mortality, more complete adjustment resulted in higher effect estimates. These analyses thus support that for two important causes of death, the lack of complete confounder information in the full cohort, probably has not resulted in overestimation of the air pollution relative risk.

Table 2 . Results case-cohort and full cohort analyses for exposure model with BS background concentration (period 1987-1996) and the traffic intensity on the nearest road with different confounder models to evaluate whether there is a selection-effect. The “start”-confounder model is the model that is used in the full cohort analyses (age, gender, active smoking, neighborhood SES and COROP area SES), to this start-model various additional confounder variables have been added separately. Added confounder variables to the full cohort confounder model are variables with p-value < 0.2 in the statistical model with all possible confounders included for total mortality. If RRs in columns 1 and 3 are similar there is no selection-effect and then RRs in columns 2, 4 and 5 can be compared.

					<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
					<b>Unadjusted case-cohort analyses*</b>	<b>Adjusted case-cohort analyses using described confounder model*</b>	<b>Unadjusted case-cohort analyses with all observations</b>	<b>Adjusted case-cohort analyses with full cohort confounder model</b>	<b>Adjusted full cohort analyses with full cohort confounder model</b>
					* Similar N	* Similar N			
<b>Confounder model</b>	<b>Exposure model</b>	<b>Cause</b>	<b>N case-cohort</b>	<b>%</b>	<b>RR</b>	<b>RR</b>	<b>RR</b>	<b>RR</b>	<b>RR</b>
Full cohort confounder model	Background BS	Total	20147	100	1.17 (0.99-1.39)	1.07 (0.87-1.32)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				0.99 (0.91-1.07)	0.97 (0.90-1.06)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
Full cohort confounder model	Background BS	Cardiopulm	11034	100	1.19 (0.97-1.45)	1.08 (0.84-1.38)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.00 (0.91-1.10)	0.99 (0.90-1.09)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
Full cohort confounder model	Background BS	Lung cancer	6284	100	1.14 (0.86-1.52)	0.97 (0.67-1.39)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.01 (0.90-1.14)	0.99 (0.88-1.12)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
Full cohort confounder model	Background BS	Non-cardio	12308	100	1.16 (0.97-1.38)	1.08 (0.88-1.34)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.96 (0.88-1.05)	0.95 (0.87-1.04)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
Full cohort confounder model	Background BS	Respiratory	5508	100	1.40 (0.98-2.01)	1.19 (0.78-1.82)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				1.01 (0.88-1.16)	1.00 (0.88-1.14)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ education	Background BS	Total	19927	98.9	1.16 (0.97-1.37)	1.09 (0.88-1.35)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				0.98 (0.90-1.07)	0.98 (0.90-1.06)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ education	Background BS	Cardiopulm	10909	98.9	1.17 (0.95-1.43)	1.10 (0.86-1.42)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.00 (0.90-1.10)	1.00 (0.91-1.09)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ education	Background BS	Lung cancer	6231	99.2	1.12 (0.84-1.49)	1.02 (0.70-1.47)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.02 (0.90-1.15)	1.02 (0.91-1.15)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ education	Background BS	Non-cardio	12173	98.9	1.15 (0.96-1.37)	1.09 (0.88-1.36)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)

	Traffic intensity				0.95 (0.87-1.04)	0.94 (0.86-1.03)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ education	Background BS	Respiratory	5446	98.9	1.40 (0.97-2.01)	1.28 (0.83-1.98)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				0.99 (0.86-1.14)	1.00 (0.87-1.14)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ number & years cigarettes	Background BS	Total	18754	93.1	1.16 (0.97-1.39)	1.02 (0.82-1.27)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				0.97 (0.89-1.06)	0.96 (0.88-1.04)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ number & years cigarettes	Background BS	Cardiopulm	10293	93.3	1.16 (0.94-1.43)	1.03 (0.79-1.33)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				0.99 (0.89-1.09)	0.98 (0.89-1.07)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ number & years cigarettes	Background BS	Lung cancer	5849	93.1	1.21 (0.90-1.64)	0.98 (0.66-1.47)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				0.99 (0.88-1.11)	0.98 (0.87-1.11)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ number & years cigarettes	Background BS	Non-cardio	11584	94.1	1.14 (0.95-1.37)	1.03 (0.82-1.28)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.95 (0.87-1.03)	0.93 (0.86-1.02)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ number & years cigarettes	Background BS	Respiratory	5184	94.1	1.30 (0.90-1.88)	1.01 (0.65-1.59)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				0.97 (0.84-1.13)	0.97 (0.83-1.13)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ occupational exposure	Background BS	Total	17299	85.9	1.15 (0.96-1.38)	1.09 (0.86-1.37)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				0.97 (0.89-1.06)	0.96 (0.88-1.05)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ occupational exposure	Background BS	Cardiopulm	9520	86.3	1.20 (0.97-1.49)	1.12 (0.86-1.47)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				0.97 (0.88-1.07)	0.96 (0.87-1.06)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ occupational exposure	Background BS	Lung cancer	5405	86.0	1.12 (0.82-1.52)	1.00 (0.67-1.50)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.01 (0.89-1.14)	1.01 (0.89-1.15)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ occupational exposure	Background BS	Non-cardio	10549	85.7	1.11 (0.92-1.35)	1.08 (0.85-1.37)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.95 (0.87-1.04)	0.94 (0.86-1.03)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ occupational exposure	Background BS	Respiratory	4749	86.2	1.48 (1.00-2.18)	1.58 (0.98-2.56)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				0.98 (0.84-1.13)	0.97 (0.84-1.12)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ passive smoking	Background BS	Total	18184	90.3	1.20 (1.00-1.43)	1.06 (0.85-1.32)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				0.98 (0.89-1.07)	0.97 (0.89-1.05)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ passive smoking	Background BS	Cardiopulm	9948	90.2	1.23 (0.99-1.51)	1.08 (0.83-1.41)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				0.99 (0.89-1.09)	0.98 (0.89-1.08)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ passive smoking	Background BS	Lung cancer	5712	90.9	1.17 (0.87-1.58)	0.97 (0.66-1.42)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				0.98 (0.86-1.10)	0.96 (0.85-1.09)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ passive smoking	Background BS	Non-cardio	11063	89.9	1.17 (0.97-1.42)	1.07 (0.85-1.34)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)

	Traffic intensity				0.96 (0.88-1.05)	0.95 (0.87-1.04)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ passive smoking	Background BS	Respiratory	4970	90.2	1.40 (0.96-2.04)	1.17 (0.75-1.84)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				0.99 (0.86-1.15)	0.99 (0.86-1.14)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ BMI	Background BS	Total	19357	96.1	1.12 (0.94-1.34)	1.02 (0.82-1.27)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				0.99 (0.90-1.08)	0.98 (0.89-1.07)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ BMI	Background BS	Cardiopulm	10592	96.0	1.14 (0.93-1.40)	1.02 (0.79-1.32)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.01 (0.91-1.11)	1.00 (0.90-1.10)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ BMI	Background BS	Lung cancer	6064	96.5	1.12 (0.83-1.50)	0.93 (0.64-1.34)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.02 (0.91-1.16)	1.00 (0.88-1.14)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ BMI	Background BS	Non-cardio	11841	96.2	1.10 (0.92-1.32)	1.03 (0.83-1.29)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.95 (0.87-1.04)	0.94 (0.86-1.03)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ BMI	Background BS	Respiratory	5291	96.1	1.42 (0.98-2.05)	1.18 (0.75-1.84)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				0.99 (0.86-1.14)	0.96 (0.81-1.13)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ cigar smoking	Background BS	Total	19433	96.5	1.14 (0.96-1.36)	1.07 (0.86-1.32)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				1.02 (0.94-1.11)	1.00 (0.92-1.09)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ cigar smoking	Background BS	Cardiopulm	10669	96.7	1.16 (0.94-1.42)	1.10 (0.86-1.41)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.06 (0.96-1.16)	1.04 (0.94-1.14)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ cigar smoking	Background BS	Lung cancer	6063	96.5	1.14 (0.85-1.53)	0.95 (0.65-1.38)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.08 (0.95-1.23)	1.03 (0.90-1.18)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ cigar smoking	Background BS	Non-cardio	11931	96.9	1.13 (0.94-1.360)	1.06 (0.85-1.32)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.97 (0.89-1.07)	0.96 (0.87-1.06)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ cigar smoking	Background BS	Respiratory	5342	97.0	1.37 (0.95-1.99)	1.25 (0.81-1.94)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				1.08 (0.93-1.26)	1.05 (0.91-1.22)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ pipe smoking	Background BS	Total	19531	96.9	1.19 (1.00-1.41)	1.09 (0.88-1.35)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				1.02 (0.94-1.12)	1.00 (0.92-1.09)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ pipe smoking	Background BS	Cardiopulm	10729	97.2	1.21 (0.99-1.49)	1.12 (0.87-1.44)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.06 (0.96-1.16)	1.03 (0.93-1.13)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ pipe smoking	Background BS	Lung cancer	6108	97.2	1.16 (0.86-1.56)	0.97 (0.67-1.41)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.08 (0.95-1.24)	1.03 (0.90-1.18)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ pipe smoking	Background BS	Non-cardio	11975	97.2	1.16 (0.97-1.39)	1.08 (0.87-1.34)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)

	Traffic intensity				0.98 (0.89-1.07)	0.96 (0.87-1.05)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ pipe smoking	Background BS	Respiratory	5375	97.6	1.46 (1.01-2.11)	1.30 (0.84-2.00)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				1.08 (0.92-1.26)	1.04 (0.89-1.21)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ alcohol use	Background BS	Total	18928	93.9	1.15 (0.97-1.38)	1.02 (0.82-1.27)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				1.01 (0.92-1.10)	1.00 (0.92-1.10)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ alcohol use	Background BS	Cardiopulm	10349	93.8	1.17 (0.95-1.45)	1.05 (0.81-1.36)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.02 (0.92-1.13)	1.02 (0.93-1.13)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ alcohol use	Background BS	Lung cancer	5982	95.2	1.10 (0.82-1.47)	0.87 (0.60-1.26)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.02 (0.90-1.15)	1.00 (0.87-1.14)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ alcohol use	Background BS	Non-cardio	11574	94.0	1.15 (0.95-1.38)	1.04 (0.83-1.30)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.98 (0.89-1.07)	0.97 (0.89-1.07)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ alcohol use	Background BS	Respiratory	5202	94.4	1.39 (0.96-2.02)	1.12 (0.72-1.75)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				1.02 (0.88-1.17)	1.02 (0.88-1.18)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ dietary variables	Background BS	Total	18225	90.5	1.09 (0.91-1.30)	1.01 (0.81-1.26)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				1.03 (0.94-1.13)	1.02 (0.93-1.12)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ dietary variables	Background BS	Cardiopulm	10001	90.6	1.10 (0.89-1.35)	1.02 (0.79-1.33)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.06 (0.96-1.18)	1.06 (0.95-1.17)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ dietary variables	Background BS	Lung cancer	5815	92.5	1.09 (0.80-1.47)	0.93 (0.64-1.37)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.08 (0.93-1.24)	1.04 (0.90-1.20)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ dietary variables	Background BS	Non-cardio	11253	91.4	1.08 (0.89-1.30)	1.02 (0.81-1.28)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)
	Traffic intensity				0.99 (0.89-1.09)	0.97 (0.88-1.08)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ dietary variables	Background BS	Respiratory	5097	92.5	1.22 (0.83-1.78)	1.18 (0.75-1.86)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				1.10 (0.93-1.30)	1.07 (0.90-1.27)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)
+ all above variables (excl diet)	Background BS	Total	13283	65.9	1.09 (0.89-1.35)	1.02 (0.82-1.27)	1.15 (0.97-1.35)	1.07 (0.87-1.32)	1.09 (1.00-1.19)
	Traffic intensity				1.01 (0.91-1.12)	0.98 (0.89-1.07)	0.99 (0.91-1.08)	0.97 (0.90-1.06)	1.03 (1.00-1.08)
+ all above variables (excl diet)	Background BS	Cardiopulm	7369	66.8	1.14 (0.89-1.46)	1.09 (0.79-1.50)	1.17 (0.97-1.42)	1.08 (0.84-1.38)	1.12 (0.98-1.28)
	Traffic intensity				1.03 (0.91-1.16)	1.03 (0.91-1.17)	1.01 (0.92-1.11)	0.99 (0.90-1.09)	1.06 (1.00-1.12)
+ all above variables (excl diet)	Background BS	Lung cancer	4239	67.5	1.08 (0.76-1.54)	1.04 (0.63-1.70)	1.17 (0.89-1.53)	0.97 (0.67-1.39)	1.01 (0.78-1.32)
	Traffic intensity				1.06 (0.92-1.23)	1.05 (0.89-1.23)	1.00 (0.89-1.13)	0.99 (0.88-1.12)	1.07 (0.96-1.19)
+ all above variables (excl diet)	Background BS	Non-cardio	8167	66.4	1.05 (0.84-1.31)	0.96 (0.73-1.26)	1.12 (0.94-1.33)	1.08 (0.88-1.34)	1.09 (0.96-1.23)

	Traffic intensity				0.97 (0.86-1.09)	0.95 (0.84-1.08)	0.97 (0.89-1.05)	0.95 (0.87-1.04)	1.00 (0.94-1.06)
+ all above variables (excl diet)	Background BS	Respiratory	3731	67.7	1.45 (0.92-2.29)	1.53 (0.84-2.81)	1.42 (1.01-2.00)	1.19 (0.78-1.82)	1.22 (0.86-1.74)
	Traffic intensity				1.00 (0.80-1.25)	0.94 (0.70-1.27)	1.04 (0.91-1.19)	1.00 (0.88-1.14)	1.10 (0.95-1.26)

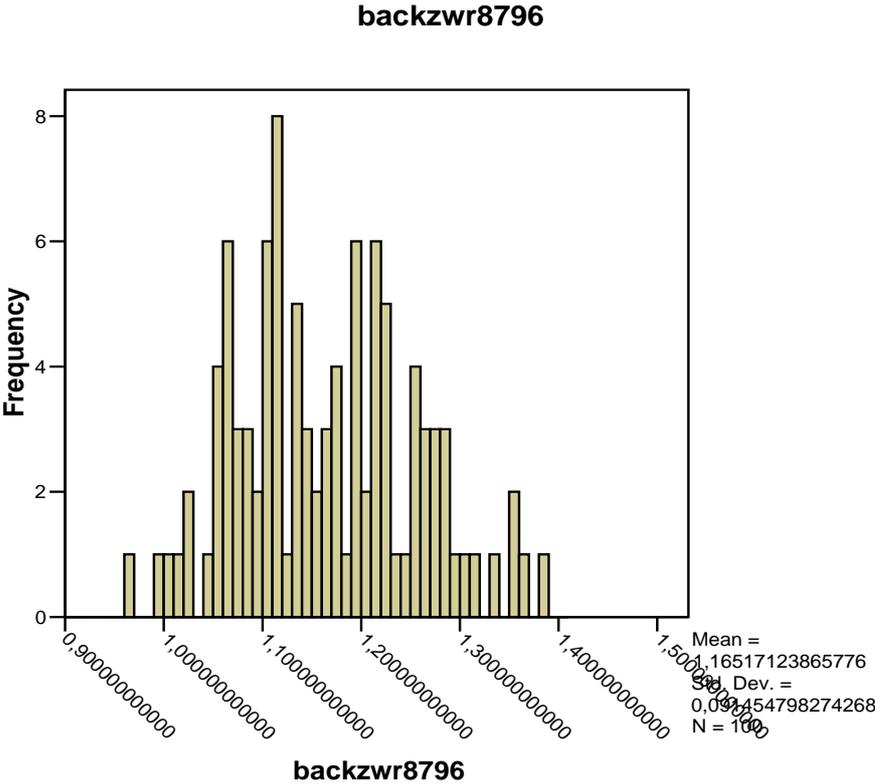
As shown in table 1, the age and gender adjusted results of the case cohort and the full cohort analyses produced nearly identical results for background black smoke concentrations but not for traffic intensity on nearest road. This variable was positively associated with total and cardiopulmonary mortality in the full cohort analysis but there was no association in the case cohort analysis. We further explored this issue by randomly generating one hundred subcohorts of 5,000 subjects from the study population, and then repeating the age and gender adjusted case cohort analysis using each of these 100 subcohorts in turn as reference. The results are shown in table 3 and figure 1. They indicate that for traffic intensity on the nearest road and living near a major road the results of the age and gender adjusted case cohort analysis using the original subcohort is lower the average of the 100 randomly drawn subcohorts. For traffic intensity in a 100 m buffer, there was no such difference. These results suggest that for the exposure variables ‘living near a busy road’ and ‘traffic intensity on nearest road’, the effect estimates are sensitive to the selection of the subcohort even though it was completely random. For the exposure variables including ‘traffic intensity in a 100 m buffer’ and background Black Smoke the differences between the three approaches were marginal. These results suggest that for two of the three ‘traffic’ variables, the case cohort analysis using the original subcohort produced effect estimates which do not reflect the underlying effect estimates in the study population as a whole.

Table 3. Distribution of age and gender adjusted relative risk estimates for cardiopulmonary mortality from case-cohort analyses of 100 randomly selected subcohorts, of the case-cohort analyses with original subcohort and RRs of the full cohort analyses.

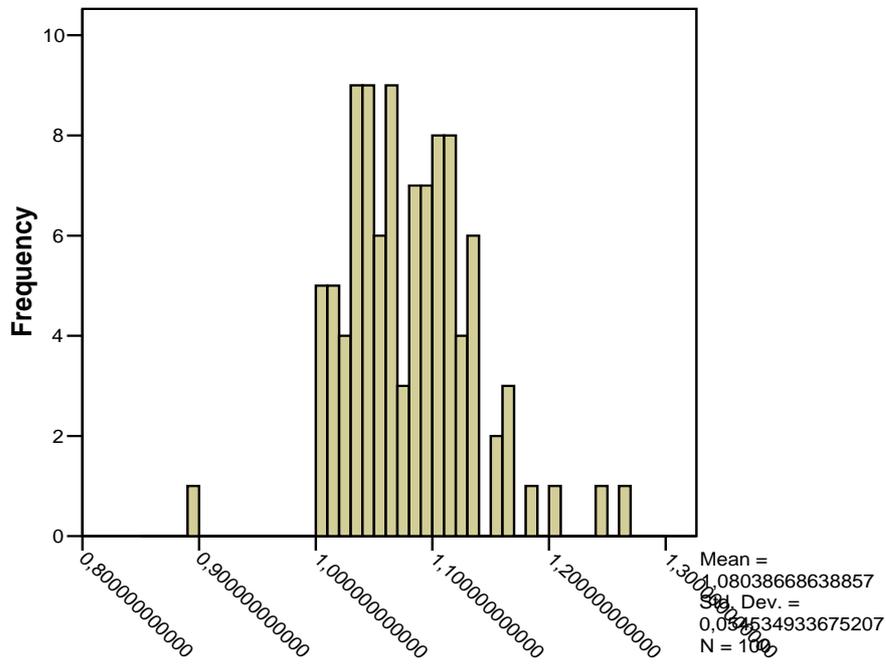
<b>Exposure model</b>	<b>RR (95%-CI) for case-cohort with original subcohort</b>	<b>RR (95%-CI) for full cohort</b>	<b>Average RR of 100 case-cohort analyses (minimum, maximum)</b>
Black smoke background	1.17 (0.97 – 1.42)	1.17 (1.05 – 1.30)	1.16 (0.97 – 1.38)
Traffic intensity on nearest road	1.01 (0.92 – 1.11)	1.07 (1.02 – 1.13)	1.08 (0.90 – 1.26)
Black smoke background	1.13 (0.93 – 1.38)	1.16 (1.04 – 1.29)	1.15 (0.94 – 1.41)
Traffic intensity in a 100 m buffer	1.08 (0.95 – 1.22)	1.06 (0.99 – 1.14)	1.07 (0.89 – 1.21)
Black smoke background	1.18 (0.97 – 1.42)	1.18 (1.06 – 1.31)	1.17 (0.98 – 1.39)
Living near a major road	1.00 (0.83 – 1.21)	1.10 (0.99 – 1.22)	1.10 (0.84 – 1.37)

In summary, results of the adjusted case-cohort analyses are difficult to interpret because of a combination of random variability introduced by sampling from the full cohort and selection due to missing values in the complete confounder model. Probably the limited availability of confounders in the full cohort analyses does not result in substantial residual confounding in the adjusted effect estimates. We therefore focus our interpretation mostly on the full cohort results and use the case-cohort analyses for more specific analyses (effect modification, moving during follow-up).

Figure 1 Distribution of age and gender adjusted relative risks for cardiopulmonary mortality from case-cohort analyses of 100 randomly selected subcohorts of Black Smoke concentration (background and overall=sum) and traffic variables (traffic nearest road, living near a major road, traffic in 100 meter buffer)

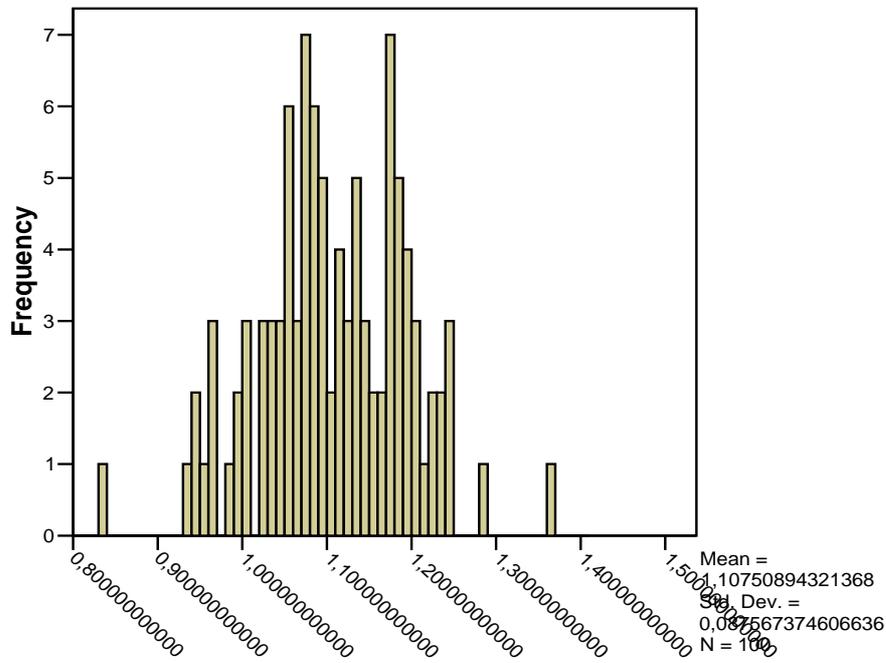


**inear86a**



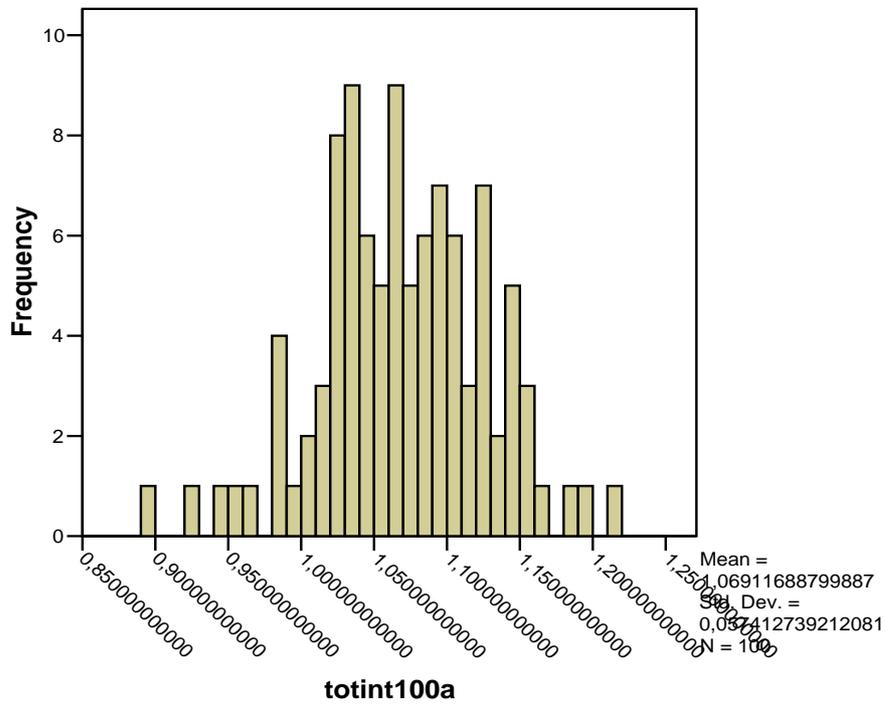
**inear86a**

**major**

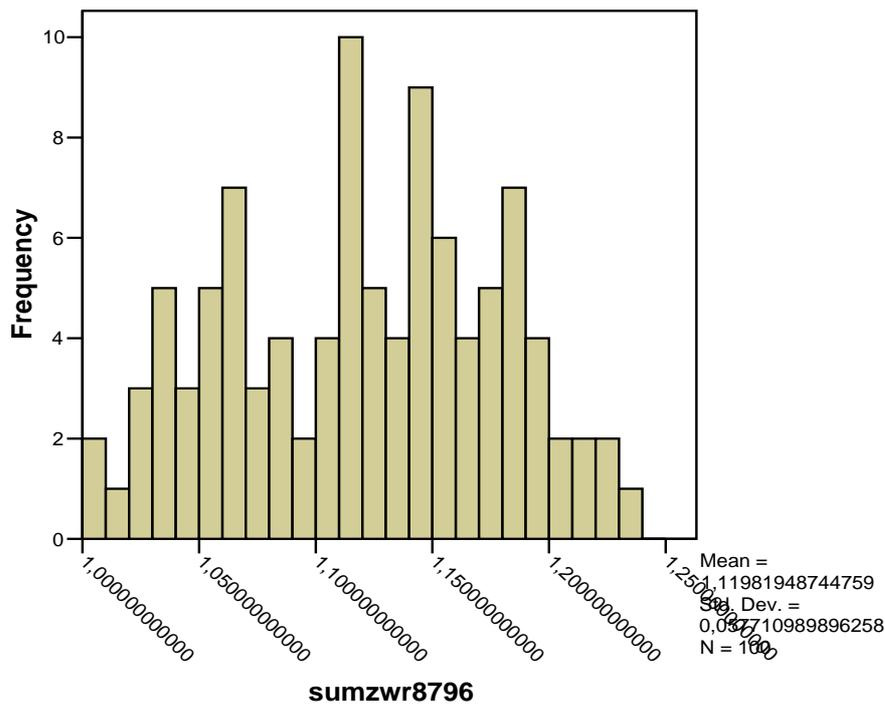


**major**

**totint100a**



**sumzwr8796**



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