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26. Risk Assessment for Inhomogeneous Subgroups

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"Risk" has different meanings in our daily language. We speak of risk if a situation could have a negative outcome, e.g., if we could lose money in business or our life in an adventure. In epidemiology such a situation is called a "risk factor" or better "risk condition" (as it is not always clear whether the specific conditions of the situation really "make" the negative outcome). "Risk" is understood quantitatively as the probability or chance for the negative event in presence of the specific conditions. This implies that risk is considered for populations where the specific conditions are present as well as absent. Let us assume, as a specific condition, environmental tobacco smoke (ETS) and, as a negative event, lung cancer (LC); the data layout for risk calculations is given in Table 26.1.

N_1 individuals of the population are exposed to ETS and N_0 are not exposed. From the exposed individuals E_1 show the event (LC) (and $F_1 = N_1 - E_1$ do not). The risk for LC in the exposed group is the ratio $R_1 = E_1/N_1$. Analogous in the nonexposed group, the risk for LC is the ratio $R_0 = E_0/N_0$, if E_0 LCs occurred under the N_0 individuals not exposed to ETS.

As a measure of the risk involved with the condition (ETS), usually the "relative risk" is computed, i.e., the ratio of the risk rate for the exposed individuals to the rate for the nonexposed individuals (reference group). As can be seen in Table 26.1, this ratio can be interpreted either as the ratio of the "observed" number of events (LC) in the exposed group to the "expected" number if the risk ratio of the reference group is applied to the exposed group; or the ratio of the expected number in the reference group to the observed number in this group if the risk ratio of the exposed group is applied to the reference group. The expected numbers are also called "standardized" numbers. For the crude relative risk, either the exposed or the reference group can be used for standardization.

The relative risk is a factor indicating by how much the risk ratio in the exposed group is higher (or lower) than that in the reference group. This figure may be misleading, especially if the risk ratios for both groups are small. A relative risk of 2 or 3 suggests a very high risk, but even for the exposed group the

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Table 26.1. Data layout for crude relative risk.

	Risk (ETS)	Reference (NETS)
Event (LC)	E_1	E_0
No event (NLC)	F_1	F_0
Size (# ind.)	N_1	N_0

Risk rate for ETS: $R_1 = E_1/N_1$
Risk rate for NETS: $R_0 = E_0/N_0$
Crude relative risk for ETS: $CRR_1 = R_1/R_0 = (E_1 \cdot N_0)/(E_0 \cdot N_1) = E_1/[(N_1 \cdot (E_0/N_0)] = /N_0 \cdot (E_1/N_1)]/E_0$
Crude attributable risk for ETS: $CAR_1 = R_1 - R_0$

real risk, i.e., the risk ratio, may be relatively small. A measure which better reflects the magnitude of the risk associated with a specified risk condition is the "attributable risk," i.e., the difference between the risk ratio in the exposed and that in the reference group.

The relationship among the different risk measures can be demonstrated using Hirayama's data (1984a) about LC mortality in nonsmoking women with smoking husbands (Table 26.2). The risk ratio for the exposed is 2.34 per 1000 individuals and for the reference group it is 1.69 per 1000. The (crude) relative risk is 1.38, the (crude) attributable risk is 0.69 per 1000.

It is usually assumed that the attributable risk gives, for each individual of the population, that part of the risk which can be attributed solely to the risk factor. This assumption is only true if the risk ratios for the total population are not confounded or biased by other factors or conditions. In practice, such confounding conditions are always present in populations. The most relevant confounding condition is age. The population has different age groups or strata, and in general the risk ratios for the exposed and reference group vary within the strata. The situation is represented in the general data layout of Table 26.3.

It is assumed that the total population is split up in J subgroups according to one or more confounding conditions such as age. In addition, it is assumed that more than one risk condition (exposure condition) is distinguished (e.g., different times or extents of exposure). Each subgroup is homogeneous with respect to the

Table 26.2. Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. (From Hirayama 1984a).

	ETS	NETS
LC	163	37
NLC	69,462	21,858
Size	69,645	21,895

$R_1 = 0.00234$
$R_0 = 0.00169$
$CRR_1 = 1.38$
$CAR_1 = 0.00234 - 0.00169 = 0.00065$

Table 26.3. Data layout for risk conditions C_i ($i = 1, \ldots I$) and reference condition C_0 in a population composed of J strata with levels S_j ($j = 1, \ldots J$).

Stratum	Components of risk rate	Category of risk condition C_1 ... C_i ... C_I	Reference condition C_0	Relative risk
		. ...	.	
S_1		. ...	.	
		. ...	.	
	Event	. ... E_{ij}	E_{0j}	$RR_{ij} =$
S_j	No event	. ... F_{ij}	F_{0j}	$(E_{ij}/N_{ij})/$
	Size	. ... N_{ij}	N_{0j}	(E_{0j}/N_{0j})
		. ...	.	
S_J		. ...	.	
		. ...	.	
Total population	Event	. ... E_i	E_0	$CRR_i =$
	No event	. ... F_i	F_0	$(E_i/N_i)/$
	Size	. ... N_i	F_0	(E_o/N_0)

confounding condition. Therefore, the risk ratios and relative risks within the subgroups reflect the real risk for the respective individuals. However, the risks among the subgroups are inhomogeneous. Calculating the crude risks from the population totals may produce serious biases. The question is how the risk ratios or relative risks of the different strata can be combined to give a meaningful "overall" measure of the risk for the population.

One approach in solving this question is "standardization." Table 26.4 presents the most common standardized relative risks. Very often the "standardized mortality (morbidity) ratio" is used as a measure of overall risk. As can be seen from Table 26.4, in each stratum (e.g., age group) the observed risk ratios of the exposed and reference groups are standardized to the distribution of the confounding condition (e.g., age distribution) in the respective *exposed* group. This is not the best idea, as Miettinen (1972) has pointed out. A better idea is to standardize to the *reference* group. The result is the "standardized reference risk."

In general, one has to take a relevant standard distribution A_j and standardize all the exposed and the reference risks to this distribution. For cohort studies, an appropriate standard distribution is the distribution of the confounding factor in the population from which the cohort is sampled, e.g., the age distribution of the population.

As can be seen from Table 26.4, the standardized relative risk is a weighted average of the relative risks within the strata. The weights depend on the selected standard distribution A_j and the risk ratios in the reference group.

As "internal" standard distributions, the distribution of the confounding condition in the total cohort or the harmonic mean of the distributions in the exposed and reference group is of special interest. The latter is equivalent to the standardization proposed by Mantel and Haenszel (1959). The relationship among

Table 26.4. Combining the risk ratios of the strata to an overall risk.

Standardized mortality (morbidity) ratio SMR_i (strata distribution in risk population as standard)

$$SMR_i = E_i/\Sigma_j N_{ij} \cdot (E_{0j}/N_{0j})$$
$$= \Sigma_j N_{ij} \cdot (E_{ij}/N_{ij})/\Sigma_j N_{ij} \cdot (E_{0j}/N_{0j})$$

Standardized reference risk SRR_i (strata distribution in reference population as standard)

$$SRR_i = \Sigma_j N_{0j} \cdot (E_{ij}/N_{ij})/\Sigma_j N_{0j} \cdot (E_{0j}/N_{0j})$$
$$= \Sigma_j N_{0j} \cdot (E_{ij}/N_{ij})/E_0$$

Standardized general risk $SRR(A)_i$ (general strata distribution A_j as standard)

$$SRR(A)_i = \Sigma_j A_j \cdot (E_{ij}/N_{ij})/\Sigma_j A_j \cdot (E_{0j}/N_{0j})$$
$$= \Sigma_j (A_j \cdot (E_{0j}/N_{0j}) \cdot RR_{ij}/\Sigma_j A_j \cdot (E_{0j}/N_{0j})$$
$$= \Sigma_j G_j \cdot RR_{ij}$$

$$\text{with } RR_{ij} = (E_{ij}/N_{ij})/(E_{0j}/N_{0j})$$
$$\text{and the "weights"} \quad G_j = A_j \cdot (E_{0j}/N_{0j})/\Sigma_j A_j \cdot (E_{0j}/N_{0j})$$

Special "internal standards":
Cohort total standard:

$$A_j = N_{ij} + N_{0j} \; (= \Sigma_{i=0\ldots I} N_{ij}) = N_j$$
$$G_j = [(N_j/N_{0j}) \cdot E_{0j}]/[\Sigma_j (N_j/N_{0j}) \cdot E_{0j}]$$

$$SRR(N)_i = \Sigma_j N_j \cdot (E_{ij}/N_{ij})/\Sigma_j N_j \cdot (E_{0j}/N_{0j})$$

Harmonic mean (Mantel-Haenszel) standard:

$$A_j = (N_{ij} \cdot N_{0j}/N_j \; [= N_{0j} \cdot (\Sigma_{i=1\ldots I} N_{ij})/N_j]$$
$$G_j = [(N_{ij}/N_j) \cdot E_{0j})/[\Sigma_j (N_{ij}/N_j) \cdot E_{0j}]$$

$$SRR(MH)_i = [\Sigma_j (E_{ij} \cdot N_{0j})/N_j]/[\Sigma_j (E_{0j} \cdot N_{ij})/N_j]$$

the various standardized risks is discussed by Ahlborn et al. (1988). The use of these different standardized risks can be demonstrated using the results of Hirayama's (1984b) cohort study of ETS and LC in nonsmoking Japanese women. The age of the women (at study entry) is used as a confounding condition. The age distribution of married women in the Japanese population is used as an exter-

Table 26.5. Hirayama's data stratified to wife's age. (From Hirayama 1984b).

Stratum –wife's age (years)	Category of risk condition (husband's smoking habits) 1–19 cigarettes LC	1–19 cigarettes Size	20+ cigarettes LC	20+ cigarettes Size	Reference condition nonsmoker LC	nonsmoker Size	Total cohort LC	Total cohort Size	A_j age distribution in population
40–49	21	17492	21	12615	4	7918	46	38025	42612
50–59	46	15640	31	8814	14	7635	91	32089	29101
60–69	31	10381	10	3793	16	6170	57	20344	15315
70–79	1	671	2	239	3	172	6	1082	4512
	99	44184	64	25461	37	21895	200	91540	91540

Table 26.6. Risk calculations with Hirayama's (1984b) data.

	Risk category 1: 1–19 cigarettes		Risk category 2: 20+ cigarettes	
Crude risks	CRR_1	= 1.32591	CRR_2	= 1.48747
Standardized mortality ratio	SMR_1	= 1.30026	SMR_2	= 1.75154
Standardized reference risk	SRR_1	= 1.36873	SRR_2	= 1.56055
Cohort total standard	$SRR(N)_1$	= 1.35220	$SRR(N)_2$	= 1.59577
Mantel-Haenszel standard (common)	$SRR(MHC)_1$	= 1.37029	$SRR(MHC)_2$	= 1.57941
Mantel-Haenszel standard (single)	$SRR(MHS)_1$	= 1.33123	$SRR(MHS)_2$	= 1.71231
Age distribution of population as standard	$SRR(A)_1$	= 0.97882	$SRR(A)_2$	= 1.30068

nal standard (data from Ahlborn et al. 1988). The age distribution of the population is related to the sample size of 91 540 in Hirayama's cohort. As can be seen from Table 26.5, there are some deviations between the age distribution of the cohort and that of the population. In Table 26.6 the risk calculations are presented for the two risk categories (husband is ex-smoker or smokes fewer than 20 cigarettes per day; husband smokes more than 20 cigarettes per day).

There are marked deviations between the standardized risks for both categories. The lowest relative risks are obtained if the age distribution in the population is used as a standard. In this case, the standardized relative risk in the lower risk category (fewer than 20 cigarettes) is slightly below 1. For the higher risk category (20 and more cigarettes) the standardized mortality ratio is remarkably increased. This shows the influence of the age distribution in the exposed group. The Mantel-Haenszel standard is calculated using the common harmonic mean of all risk categories and the reference as well as the single harmonic mean of the respective risk category and the reference. The first procedure is preferable as the risks for different categories are comparable in this case.

The question of which standardization procedure should be used depends on the aim of the risk calculations. If the risk is to be extrapolated to a population, the distribution of the confounding conditions in this population seems most appropriate. This question plays an important role in the so-called meta-analyses, i.e., for quantitative comparisons of different studies. To make the results of the different studies comparable, they must be standardized to a common external

Table 26.7. Interaction between risk conditions and confounding conditions. RR_{ij} are different for different strata S_j. Example: Hirayama's (1984b) data stratified to wife's age.

Wife's age (years)	Husband's smoking habits 1–19 cigarettes R_{1j}	1–19 cigarettes RR_{1j}	20+ cigarettes R_{2j}	20+ cigarettes RR_{2j}	Reference condition nonsmoker R_{0j}	nonsmoker R_{0j}
40–49	0.00120	2.37649	0.00166	3.29524	0.00051	1.00000
50–59	0.00294	1.60399	0.00352	1.91809	0.00183	1.00000
60–69	0.00299	1.15156	0.00264	1.01668	0.00259	1.00000
70–79	0.00149	0.08544	0.00837	0.47978	0.01744	1.00000

Table 26.8. Logistic regression analysis applied to Hirayama's (1984b) data—without interactions: $\log(R_{ij}/(1-R_{ij})) = a_0 + c_1C_1 + \ldots + s_1S_1$.

Main effects	Estimated odds ratio
Husband's smoking habits ($P = 0.049$):	
Nonsmoker	0.765
1–19 cigarettes	1.033
20+ cigarettes	1.265
Age (years) ($P = 0.000$):	
40–49	0.437
50–59	1.047
60–69	1.074
70–79	2.036

standard distribution of the confounding conditions. Unfortunately, in most of the meta-analyses of studies on ETS and health risk this is not done.

As was pointed out in Table 26.4, standardized relative risks are weighted averages of the relative risks in the strata. Such an averaging has a real basis if the relative risks within the strata are similar for the total population. If this is not the case, *interaction* between the confounding condition and the risk conditions is present. I doubt whether in this case any averaged overall risk can be interpreted meaningfully.

Let us investigate the interaction using Hirayama's (1984b) data. In Table 26.7 the relative risks for both risk categories are presented for each stratum. We see remarkable inhomogeneities in the relative risks for different strata. The highest relative risk is in the age group of 40–49 years. With increasing age, the relative risk decreases and, for the highest age group, declines remarkably to below 1. This is the result of the controversial behavior of the risk ratios in the reference and exposed groups. Whereas in the reference group the risk ratio for LC increases with increasing age, in the exposed group there is a decrease, especially for the low-risk category. One can only speculate about the reasons for this. Certainly, a selection effect (which is indicated by discrepancies in the age distributions between the cohort and the population) plays some role. Whether additional effects (e.g., a "competing risk" for other causes of death) are involved cannot be analyzed from the data available.

A method to handle interaction is the *logistic regression analysis*. With this method, it is assumed that the logarithms of the odds ratios for each combination of risk condition and confounding condition is a linear function of these variables. If the variables are qualitative, they are expressed by "indicator variables" (with a value of 1 if the quality of the variable is present, and 0 otherwise). Interactions are included in this model by product terms resulting from variables for risk conditions and confounding conditions.

I applied this technique to Hirayama's (1984b) data (Tables 26.8 and 26.9). If no interactions are included in the model, analysis shows a significant ($P = 0.049$) risk effect of a husband's smoking habits to a woman's LC and a very

Table 26.9. Logistic regression analysis applied to Hirayama's (1884b) data—with interactions: $\log(R_{ij}/(1-R_{ij})) = a_0 + c_1C_1 + \ldots + s_1S_1 + \ldots + b_{11}C_1S_1 + \ldots$

Main effects	Estimated odds ratio
Husband's smoking habits ($P = 0.265$):	
Nonsmoker	0.990
1–19 cigarettes	0.772
20+ cigarettes	1.309
Age (years) ($P = 0.000$):	
40–49	0.388
50–59	1.034
60–69	1.060
70–79	2.348

Interactions: [P (before removal) = 0.096]
[P (smoking removed) = 0.028]

	Estimated odds ratios		
Age (years)	Nonsmoker	1–19 cigarettes	20+ cigarettes
40–49	0.499	1.275	1.573
50–59	0.688	1.140	1.275
60–69	0.974	1.174	0.874
70–79	2.992	0.586	0.571

pronounced effect of age ($P = 0.000$). If interactions are included, the main effect of smoking habits is not significant, but we get a significant interaction effect ($P = 0.028$) in addition to the significant age effect. The estimated odds ratios for the interactions show very good agreement with the variation of risk ratios in Table 26.7: for younger age groups there is an increase of risk with increasing ETS, for older age groups the risk decreases.

This analysis shows that "risk" of ETS is not homogeneous in the cohort. Its extent depends on age and possibly on other factors. An overall estimate may therefore be misleading for an objective prognosis.

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The chapters in this book were originally presented as papers at a symposium held in 1989 in Hannover, FRG. They analyze data from animal exposure and human epidemiology studies for the purpose of assessing the risk posed by pollutants and establishing standards for exposure limits.

Initial chapters focus on the various approaches and problems in designing and evaluating exposure studies. A major portion of the book is devoted to the interpretation of results from such studies, the relevance of lesions in animal models to man, and the comparison of functional respiratory response among various species. The substances studied include arsenic, benzene, formaldehyde, environmental tobacco smoke, mineral fibers, asbestos, automotive exhaust emissions, and polycyclic aromatic hydrocarbons.

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