Stratification for Confounding – Part 2: Direct and Indirect Standardization

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Key Words

Confounding • Direct standardization • Indirect standardization • Stratification

Abstract

Standardization is a method used to compare observed and expected rates of a given disease/outcome by removing the influence of factors that may confound the comparison. There are two major standardization methods: one is used when the 'standard' is the structure of a population (direct method) and the other when the 'standard' is a set of specific event rates (indirect method). The direct standardization is commonly used for large populations while the indirect one is applied to populations of relatively small dimensions.

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Introduction

In a previous paper of this series, we focused on the Mantel-Haenszel method [1], a statistical technique that allows to calculate an overall, unconfounded effect estimate of a given exposure for a specific disease/outcome by pooling stratum-specific relative risks (RRs) or odds ratios. In this paper, we describe another technique based on stratification [1], termed 'standardization' that is ap-

plied to compare observed and expected rates of a given disease/outcome by removing the influence of extraneous factors (confounders) [2]. Standardization is well suited for comparing the rate of a given outcome (for example mortality) in large populations that differ for important prognostic factors like age, gender and social economical status. In such circumstances, due to the presence of confounding factors, a crude comparison of mortality rates between the two populations may be misleading [2]. There are two major standardization methods: one is used when the available 'standard' is the structure of a reference population (direct method) and the other when the 'standard' is a set of specific event rates (indirect method). For example, when controlling for gender in two populations by using direct standardization, the external standard could be set as the gender distribution derived by the combination of the two populations while in the indirect standardization the external standard is a series of gender-specific rates.

Direct Method of Standardization

Here we consider a hypothetical study investigating the mortality rate in two large populations of moderate drinkers ($n = 80,000$) and nondrinkers ($n = 80,000$). Age is a potential confounder [2] because (1) it is significantly

Table 1. Death occurrence in moderate drinkers and nondrinkers according to age strata

Age strata	Moderate drinkers (exposed)			Nondrinkers (unexposed)		
	number of individuals	number of deaths	crude mortality rate (for 100,000 individuals)	number of individuals	number of deaths	crude mortality rate (for 100,000 individuals)
<30 years	25,000	50	200	30,000	60	200
30–60 years	30,000	300	1,000	35,000	210	600
≥60 years	25,000	500	2,000	15,000	360	2,400
Total	80,000	850	1,062	80,000	630	787

The crude mortality rate (deaths/100,000 individuals) is calculated in each stratum by the standard formula: (number of deaths/number of individuals) × 100,000 (or × 10⁵).

Table 2. Observed and expected death rate in the overall population (moderate drinkers + nondrinkers)

Age strata	Proportion of deaths in moderate drinkers	Proportion of deaths in nondrinkers	Total number of individuals in each age category (moderate drinkers + nondrinkers)	Age-adjusted number of deaths in 160,000 moderate drinkers	Age-adjusted number of deaths in 160,000 nondrinkers
<30 years	0.002	0.002	25,000 + 30,000 = 55,000	0.002 × 55,000 = 110	0.002 × 55,000 = 110
30–60 years	0.01	0.006	30,000 + 35,000 = 65,000	0.01 × 65,000 = 650	0.006 × 65,000 = 390
≥60 years	0.02	0.024	25,000 + 15,000 = 40,000	0.02 × 40,000 = 800	0.024 × 40,000 = 960
			Total = 160,000	Total expected deaths = 1,560	Total expected deaths = 1,460

Table 3. Adjusted death rate in moderate drinkers and non drinkers weighted for the mean age distribution

	Adjusted death rate (for 100,000 individuals)
In moderate drinkers when weighted for the mean age distribution of moderate drinkers and nondrinkers	1,560/160,000 = 975
In nondrinkers when weighted for the mean age distribution of moderate drinkers and nondrinkers	1,460/160,000 = 912

different in the two populations (the proportion of individuals aged ≥60 years is higher in moderate drinkers than in nondrinkers; table 1), (2) it is related to the outcome of interest (mortality) and because (3) there is no scientific evidence that ageing is in the potential causal pathway mediating the link between alcohol intake and death.

As a first step, the authors stratified the two populations according to age strata and calculated the stratum-specific proportion of deaths, separately in moderate drinkers (exposed) and nondrinkers (unexposed) (table 1).

The crude mortality rate was 1,062 deaths/10⁵ in moderate drinkers and 787 deaths/10⁵ in nondrinkers. Therefore, the crude RR (that is the ratio of death rates in the exposed and unexposed groups) is 1,062/787 = 1.35. This implies that the crude mortality rate is 35% higher in moderate drinkers than in nondrinkers. If moderate drinking is causally implicated in the risk of death, the relationship between moderate alcohol intake and mortality should be independent of age (the potential confounder). To control for the confounding effect of age, the authors used the direct method of standardization. To this end, they calculated the proportion of deaths in each age category, sepa-

Table 4. Observed and expected death rate in a hypothetical sample of 545 individuals

Age categories	Observed death cases	Total number of individuals in each age category	Observed proportion of deaths	Standard death rate	Expected death cases
30–39 years	16	180	0.0889	0.0669	$0.0669 \times 180 = 12$
40–49 years	22	140	0.1571	0.0948	$0.0948 \times 140 = 13$
50–59 years	25	135	0.1852	0.1209	$0.1209 \times 135 = 16$
60–69 years	19	90	0.2111	0.1370	$0.1370 \times 90 = 12$
Total	82				53

rately in moderate drinkers and nondrinkers (see second and third columns in table 2), and summed up the stratum-specific number of individuals in the overall (combined) populations (see fourth column in table 2).

Then the authors calculated the expected, stratum-specific number of deaths in a hypothetical population of 160,000 moderate drinkers and of 160,000 nondrinkers weighed for the mean age distribution of moderate drinkers and nondrinkers (see fifth and sixth columns). Summing up the stratum-specific expected number of deaths gave 1,560 expected deaths in moderate drinkers and 1,460 expected deaths in nondrinkers. The adjusted death rates are the mortality rates that the two populations would have experienced if they had had the same distribution of the confounding factor (table 3).

By using the age-adjusted death rates, the authors calculated the age-adjusted RR of death (moderate drinking vs. nondrinking) by the standard formula:

$$\text{adjusted RR} = 975/912 = 1.07.$$

After data adjustment by age, the RR of death changed toward the null hypothesis (that is no independent effect of moderate drinking on the risk of death). Furthermore, by comparing age-adjusted ($\text{RR} = 1.07$) and unadjusted RRs ($\text{RR} = 1.35$) of death, the authors found a difference by more than 20%, a figure indicating a strong confounding effect of age. In this case, age engendered 'positive confounding' because it determined an overestimation of death risk associated with moderate alcohol intake. When using direct standardization for comparing two large populations, the statistical significance of the adjusted effect estimate ($\text{RR} = 1.07$) and the corresponding 95% confidence interval (CI) is not an issue because due to the large sample size of the two populations also a very modest risk increase (+7%) may be significant. The calculation of the 95% CI of the adjusted RR is important particularly when comparing samples of relatively small dimension (for details, see Chiang [3]).

In the renal field, the direct standardization method was used by Jager et al. [4] investigating whether the relative excess of cardiovascular over noncardiovascular mortality was higher in patients starting dialysis as compared to that in the general population in European countries. For a valid comparison, the higher age and higher percentage of males among dialysis patients had to be taken into account. To this end, age- and sex-specific mortality rates were calculated both for dialysis patients and the general population. Then, a weighted average over strata of age and sex was calculated, with the age and sex distribution of the general population in these European countries as 'standard'. By this approach, the authors found that the cardiovascular/noncardiovascular mortality rates ratio in patients starting dialysis did not differ from that in the general population.

An important limitation of the direct method of standardization is that it is inefficient when the number of categories of the confounding variable is relatively high and the sample size is relatively low. In this instance, it is preferable to use the indirect method of standardization.

Indirect Method of Standardization

In the indirect method of standardization, instead of using the distribution of the confounding variable (for example age) in a standard population, we use a series of standard age-specific rates. In this way, the expected number of deaths is calculated for each stratum of age in the population of interest. Next, the ratio of observed to expected number of deaths is taken and reported as a standardized mortality rate (SMR). Here we consider a hypothetical study including a random sample of 545 individuals in which the mortality rate was compared to that in the general, reference population (the standard death rate; table 4).

Table 5. Interpretation of SMR values

	Interpretation
SMR >1	The death risk in the population under investigation is higher than that in the reference population
SMR <1	The death risk in the population under investigation is lower than that in the reference population
SMR = 1	The death risk in the population under investigation is identical to that in the reference population

The study population was stratified according to age categories (from 30 to 69 years). In each age stratum, the authors reported the number of observed deaths, the total number of individuals, the observed proportion of deaths as well as the standard, age-specific, death rates derived from available tables of the reference population. The expected number of deaths in all age categories was calculated by multiplying the standard death rates by the number of individuals in each age stratum. By summing up the stratum-specific expected deaths, the authors found 53 total expected deaths that represent the death rate that the population under investigation would have experienced if it had had the same age-specific death rates as the reference population. The SMR is calculated by dividing the total number of observed deaths by the total number of expected deaths:

$$SMR = 82/53 = 1.55 \text{ (95\% CI = 1.23–1.92)}$$

where the 95% CI of the SMR was calculated by the standard formula (see appendix for mathematical details).

An SMR of 1.55 indicates that the death risk in the population under investigation is 55% higher than that expected if the population had experienced the same age-specific death rates as the reference population. This SMR of 1.55 is statistically significant because the corresponding 95% CI (1.23–1.92) does not include 1. This effect estimate is standardized, i.e. adjusted, for the confounding effect of age. In table 5, all possible interpretations of SMR values are given.

The indirect standardization method was applied in a recent study in Taiwan investigating the SMR for urological cancers in herbalists [5]. The SMR for urological cancers was significantly higher in Chinese herbalists as compared to the general population (SMR = 3.1, 95% CI = 1.4–5.9), and this was also true for kidney cancer (SMR = 3.8, 95% CI = 1.4–8.3) and renal failure (SMR = 2.4, 95% CI = 1.4–3.8). The authors concluded that Chi-

nese herbalists had a significantly higher risk for urological cancers as compared to the general population and emphasized the importance of safety assessments of Chinese herbs on a large scale.

Conclusions

Direct and indirect methods of standardization address confounding when comparing the rate of a given outcome (like mortality) between two populations that differ for important prognostic factors (like age, gender and social-economical status). These two methods are used for both descriptive and analytical purposes. By the direct method of standardization, we calculate adjusted mortality rates and adjusted RRs. The indirect method of standardization allows to calculate the SMR, that is the ratio between the observed number of deaths in a given population and the death rate expected assuming that the population under investigation experienced the same age-specific death rates as the reference population.

Appendix

95% CI calculation for SMR:

$$\begin{aligned} \text{Lower limit} &= \frac{Obs. \left\{ 1 - \frac{1}{9 \times Obs.} - \frac{z}{3} \left(\sqrt{\frac{1}{Obs.}} \right) \right\}^3}{Exp.} \\ \text{Upper limit} &= \frac{Obs. + 1 \left\{ 1 - \frac{1}{9 \times (Obs. + 1)} - \frac{z}{3} \left(\sqrt{\frac{1}{Obs. + 1}} \right) \right\}^3}{Exp.} \end{aligned}$$

where Obs. = number of observed deaths, Exp. = number of expected deaths and z = constant (1.96).

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