eAppendix 1. How to derive the weights of the six scenarios

Here, we provide a brief technical discussion about the weights of the six scenarios in Situations 1 and 2. **eTable 1** and **eTable 2** give the observed counts and probabilities of the four subjects, respectively. The weights of the six scenarios in Situations 1 and 2 can be obtained by using a three-variate hypergeometric distribution as:

$$
\begin{aligned}
P(x_1,x_2,x_3,x_4) &= \frac{\binom{1}{x_1}\binom{1}{x_2}\binom{1}{x_3}\binom{1}{x_4} p_{11}^{x_1} p_{01}^{(1-x_1)} p_{12}^{x_2} p_{02}^{(1-x_2)} p_{13}^{x_3} p_{03}^{(1-x_3)} p_{14}^{x_4} p_{04}^{(1-x_4)}}{\sum\limits_{x_1,x_2,x_3,x_4} \binom{1}{x_1}\binom{1}{x_2}\binom{1}{x_3}\binom{1}{x_4} p_{11}^{x_1} p_{01}^{(1-x_1)} p_{12}^{x_2} p_{02}^{(1-x_2)} p_{13}^{x_3} p_{03}^{(1-x_3)} p_{14}^{x_4} p_{04}^{(1-x_4)}} \\
&= \frac{p_{11}^{x_1} p_{01}^{(1-x_1)} p_{12}^{x_2} p_{02}^{(1-x_2)} p_{13}^{x_3} p_{03}^{(1-x_3)} p_{14}^{x_4} p_{04}^{(1-x_4)}}{\sum\limits_{x_1,x_2,x_3,x_4} p_{11}^{x_1} p_{01}^{(1-x_1)} p_{12}^{x_2} p_{02}^{(1-x_2)} p_{13}^{x_3} p_{03}^{(1-x_3)} p_{14}^{x_4} p_{04}^{(1-x_4)}}, \quad \left(\because \binom{1}{x_1}\binom{1}{x_2}\binom{1}{x_3}\binom{1}{x_4} = 1\right)
\end{aligned}
$$

where $x_1, x_2, x_3, x_4 = 0{,}1$ and $x_1 + x_2 + x_3 + x_4 = 2$.

In Situation 1, the treatment assignment of each subject is randomly determined, and the probability of the four subjects quitting smoking is uniformly $1/2$. **eTable 3** shows the joint and marginal probabilities of exposure status and subject ID in Situation 1. The weight of each scenario can be calculated as:

$$
\begin{aligned}
P(x_1,x_2,x_3,x_4) &= \frac{\left(\frac{1}{8}\right)^{x_1}\left(\frac{1}{8}\right)^{(1-x_1)}\left(\frac{1}{8}\right)^{x_2}\left(\frac{1}{8}\right)^{(1-x_2)}\left(\frac{1}{8}\right)^{x_3}\left(\frac{1}{8}\right)^{(1-x_3)}\left(\frac{1}{8}\right)^{x_4}\left(\frac{1}{8}\right)^{(1-x_4)}}{\sum\limits_{x_1,x_2,x_3,x_4}\left(\frac{1}{8}\right)^{x_1}\left(\frac{1}{8}\right)^{(1-x_1)}\left(\frac{1}{8}\right)^{x_2}\left(\frac{1}{8}\right)^{(1-x_2)}\left(\frac{1}{8}\right)^{x_3}\left(\frac{1}{8}\right)^{(1-x_3)}\left(\frac{1}{8}\right)^{x_4}\left(\frac{1}{8}\right)^{(1-x_4)}} \\
&= \frac{1}{6}.
\end{aligned}
$$

Each of the six scenarios uniformly occurs with a probability of $1/6$.

In Situation 2, we assume the probability of the males quitting smoking is $2/3$ and the probability of the females quitting smoking is $1/3$. **eTable 4** shows the joint and marginal probabilities of exposure status and subject ID in Situation 2. Therefore, the weight of each scenario can be calculated as:

$$P(x_1,x_2,x_3,x_4)=\frac{\left(\frac{1}{6}\right)^{x_1}\left(\frac{1}{12}\right)^{(1-x_1)}\left(\frac{1}{6}\right)^{x_2}\left(\frac{1}{12}\right)^{(1-x_2)}\left(\frac{1}{12}\right)^{x_3}\left(\frac{1}{6}\right)^{(1-x_3)}\left(\frac{1}{12}\right)^{x_4}\left(\frac{1}{6}\right)^{(1-x_4)}}{\sum_{x_1,x_2,x_3,x_4}\left(\frac{1}{6}\right)^{x_1}\left(\frac{1}{12}\right)^{(1-x_1)}\left(\frac{1}{6}\right)^{x_2}\left(\frac{1}{12}\right)^{(1-x_2)}\left(\frac{1}{12}\right)^{x_3}\left(\frac{1}{6}\right)^{(1-x_3)}\left(\frac{1}{12}\right)^{x_4}\left(\frac{1}{6}\right)^{(1-x_4)}}$$
$$=\frac{2^{x_1}2^{x_2}2^{(1-x_3)}2^{(1-x_4)}}{33}.$$

Consequently, scenario #1 is expected to occur with a probability of $16/33$; each of the scenarios #2–5 is expected to occur with a probability of $4/33$; and scenario #6 is expected to occur with a probability of $1/33$.

eAppendix 2. Accuracy, validity, and precision

Much epidemiologic research is devoted to obtaining an accurate estimate of disease frequency, or of the effect of exposure on a health outcome, in the source population of the study.[1] *Accuracy* in estimation implies the value of the parameter is estimated with little error. Two broad types of error afflict epidemiologic studies: systematic error and random error. Systematic errors in estimates are commonly referred to as biases; the opposite of bias is *validity*. Meanwhile, the opposite of random error is *precision*. Validity and precision are both components of accuracy.[2]

The distinction between systematic error and random error is usually explained using schematic illustrations of target shooting in introductory epidemiology textbooks.[3, 4] Suppose the parameter is the bull's-eye of a target, the estimator is the process of shooting at the target, and the individual bullet holes are estimates. Bias, or systematic error, is described as the distance between the average position of the bullet holes and the bull's-eye. This definition of bias (or more strictly speaking, exact bias[5]) can be simply shown as: $E(\hat{\theta})-\theta$, where θ is the parameter of interest and $E(\hat{\theta})$ is the expected value of an estimator $\hat{\theta}$ of the parameter θ.[6, 7] Meanwhile, variance, or random error, is described as the degree of dispersion of the bullet holes. As noted in the main text, we consider neither sampling variability nor nondeterministic counterfactuals as a source of random error in this paper; rather, we consider random error attributable to the mechanism that generates exposure events.

The relationship between accuracy, validity, and precision can be numerically described using the mean squared error (MSE) as a measure of accuracy, which is the expected value of the square of the difference between an estimator and the true value of a parameter (i.e., $E[(\hat{\theta}-\theta)^2]$).[6, 7] Note that the MSE is equal to the sum of the square of the bias (i.e., a measure of validity) and the variance of the estimator (i.e., a measure of precision),[6, 7] which can be shown as:

$$E[(\hat{\theta}-\theta)^2]=(E(\hat{\theta})-\theta)^2+E[(\hat{\theta}-E(\hat{\theta}))^2].$$

In Situation 1, the MSE is calculated as:

$$2\times\left[\frac{1}{6}\times\left\{\frac{0}{2}-\left(-\frac{1}{2}\right)\right\}^2\right]+2\times\left[\frac{1}{6}\times\left\{-\frac{1}{2}-\left(-\frac{1}{2}\right)\right\}^2\right]+2\times\left[\frac{1}{6}\times\left\{-\frac{2}{2}-\left(-\frac{1}{2}\right)\right\}^2\right]=\frac{1}{6}.$$

Because the estimator is unbiased in Situation 1 (i.e., $E(\hat{\theta})-\theta=0$), the MSE is equal to the variance of the estimator. Meanwhile, in Situation 2, the MSE is calculated as:

$$\left(\frac{16}{33}+\frac{4}{33}\right)\times\left\{\frac{0}{2}-\left(-\frac{1}{2}\right)\right\}^2+2\times\left[\frac{4}{33}\times\left\{-\frac{1}{2}-\left(-\frac{1}{2}\right)\right\}^2\right]+\left(\frac{4}{33}+\frac{1}{33}\right)\times\left\{-\frac{2}{2}-\left(-\frac{1}{2}\right)\right\}^2=\frac{25}{132},$$

which is slightly larger than the MSE in Situation 1. Unlike in Situation 1, when the estimator is biased, the square of the bias is calculated as:

$$\left\{-\frac{3}{11}-\left(-\frac{1}{2}\right)\right\}^2=\left(\frac{5}{22}\right)^2=\frac{25}{484},$$

and the variance of the estimator is calculated as:

$$\left(\frac{16}{33}+\frac{4}{33}\right)\times\left\{\frac{0}{2}-\left(-\frac{3}{11}\right)\right\}^2+2\times\left[\frac{4}{33}\times\left\{-\frac{1}{2}-\left(-\frac{3}{11}\right)\right\}^2\right]+\left(\frac{4}{33}+\frac{1}{33}\right)\times\left\{-\frac{2}{2}-\left(-\frac{3}{11}\right)\right\}^2=\frac{550}{3993}.$$

Consequently, the MSE (i.e., $25/132$) can be decomposed into the component of systematic error (i.e., $(5/22)^2=25/484$) and the component of random error (i.e., $550/3993$) in Situation 2.

In conclusion, the estimators in Situations 1 and 2 have approximately the same degree of accuracy. However, the estimator in Situation 1 has higher validity than in Situation 2. In contrast, the estimator in Situation 2 has higher precision than in Situation 1. A tradeoff between bias and variance has been called the "bias-variance dilemma".[8] Note that the above discussion holds true for any measures, although careful consideration is needed when using ratio measures (see the footnote [b] in **eTable 5**).

eAppendix 3. Mathematical definitions of the four notions of confounding

We let A denote an exposure of interest, Y an outcome of interest, and C a set of covariates. Then, we let Y_a denote the potential outcomes for an individual if exposure A had been set, possibly contrary to fact, to value a. We assume that the consistency assumption is met, which implies that the observed outcome for an individual is the potential outcome, as a function of intervention, when the intervention is set to the actual exposure.[9, 10] For simplicity, we will generally assume a binary exposure variable (1 = exposed, 0 = unexposed).

According to VanderWeele,[11] *confounding in distribution* is defined as follows:

> We say that there is no *confounding in distribution* of the effect of A on Y conditional on C if $P(Y_a \mid C=c)=P(Y \mid A=a, C=c)$ for all a, c.

We denote measures of interest by $\mu(\phi_1,\phi_0)$, which is a contrast of population parameters. When defining population causal effects, ϕ_a is a population parameter for the distributions of potential outcomes Y_a if A had been set to a for all in the target.[12] Then, according to VanderWeele,[11] *confounding in measure* is defined as follows:

> We say that there is no *confounding in measure* μ of the effect of A on Y conditional on C if $\mu\left(E(Y_1 \mid C=c), E(Y_0 \mid C=c)\right)=\mu\left(E(Y \mid A=1, C=c), E(Y \mid A=0, C=c)\right)$ for all c.

To show mathematical definitions of *confounding in expectation* and *realized confounding*, we use $P(Y_a \mid C=c)$ as a distribution of interest below. We let J_m denote a scenario of exposure allocation among the target population, which is generated by mechanism m. We also let A_j denote a binary exposure (1 = exposed, 0 = unexposed) under scenario j. Then, *confounding in expectation* can be defined as follows:

> We say that there is no *confounding in expectation* of the effect of A on Y conditional C under mechanism m if $P(Y_a \mid C=c)=E_{J_m}P(Y \mid A_{J_m}=a, C=c)$ for all a, c.

Finally, *realized confounding* can be defined as follows:

> We say that there is no *realized confounding* of the effect of A on Y conditional C under scenario j if $P(Y_a \mid C=c)=P(Y \mid A_j=a, C=c)$ for all a, c.

An analogous discussion applies when using $\mu\left(E(Y_1 \mid C=c), E(Y_0 \mid C=c)\right)$ as a measure of interest.

eReferences

e1. Greenland S, Morgenstern H. Confounding in health research. Annu Rev Public Health. 2001;22:189–212.

e2. Rothman KJ, Greenland S, Lash TL. Validity in epidemiologic studies. In: Rothman KJ, Greenland S, Lash TL, editors. Modern Epidemiology. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008. p. 128–47.

e3. Greenberg RS, Daniels SR, Flanders WD, Eley JW, Boring III JR. Medical Epidemiology. 4th ed. New York, NY. Lange Medical Books/McGraw-Hill; 2005.

e4. Jekel JF, Katz DF, Elmore JG, Wild DMG. Epidemiology, Biostatistics, and Preventive Medicine. 3rd ed. Philadelphia, PA. Saunders/Elsevier; 2007.

e5. Hernán MA, Robins JM. Causal Inference. Boca Raton, FL. Chapman & Hall/CRC; 2016 (forthcoming).

e6. Everitt B, Skrondal A. The Cambridge Dictionary of Statistics. 4th ed. Cambridge, UK. Cambridge University Press; 2010.

e7. Upton G, Cook I. A Dictionary of Statistics. 2nd ed. New York, NY. Oxford University Press; 2008.

e8. Borkar VS. There’s no such thing as a free lunch: the bias-variance dilemma. Resonance. 1998;3:40–51.

e9. Cole SR, Frangakis CE. The consistency statement in causal inference: a definition or an assumption? Epidemiology. 2009;20:3–5.

e10. VanderWeele TJ. Concerning the consistency assumption in causal inference. Epidemiology. 2009;20:880–3.

e11. VanderWeele TJ. Confounding and effect modification: distribution and measure. Epidemiol Method [Internet]. 2012 Aug [cited 2012 Aug 29]; 1(1):[55–82 p.]. Available from: http://www.degruyter.com/view/j/em.2012.1.issue-1/2161-962X.1004/2161-962X.1004.xml?format=INT

e12. Flanders WD, Klein M. A general, multivariate definition of causal effects in epidemiology. Epidemiology. 2015;26:481–9.

e13. Agresti A. Categorical Data Analysis. New York, NY. John Wiley & Sons; 1990.

eTable 1. Observed counts among the four subjects

Subject ID	Sex	Exposed	Unexposed	
Subject #1	Male	x_1	$1-x_1$	1
Subject #2	Male	x_2	$1-x_2$	1
Subject #3	Female	x_3	$1-x_3$	1
Subject #4	Female	x_4	$1-x_4$	1
		2	2	4

eTable 2. Probabilities among the four subjects

Subject ID	Sex	Exposed	Unexposed	
Subject #1	Male	p_{11}	p_{01}	1/4
Subject #2	Male	p_{12}	p_{02}	1/4
Subject #3	Female	p_{13}	p_{03}	1/4
Subject #4	Female	p_{14}	p_{04}	1/4
		1/2	1/2	1

eTable 3. Probabilities among the four subjects in Situation 1

Subject ID	Sex	Exposed	Unexposed	
Subject #1	Male	1/8	1/8	1/4
Subject #2	Male	1/8	1/8	1/4
Subject #3	Female	1/8	1/8	1/4
Subject #4	Female	1/8	1/8	1/4
		1/2	1/2	1

Probability of the four subjects quitting smoking is $1/2$, so the joint probabilities can be uniformly calculated as: $1/4 \times 1/2 = 1/8$. This table clearly shows that sex and treatment are independent in Situation 1.

eTable 4. Probabilities among the four subjects in Situation 2

Subject ID	Sex	Exposed	Unexposed	
Subject #1	Male	1/6	1/12	1/4
Subject #2	Male	1/6	1/12	1/4
Subject #3	Female	1/12	1/6	1/4
Subject #4	Female	1/12	1/6	1/4
		1/2	1/2	1

Probability of the two males quitting smoking (i.e., P[quitting | male]) is $2/3$, so the joint probability of quitting and being male can be calculated as: $1/4 \times 2/3 = 1/6$. Likewise, because the probability of the two females quitting smoking (i.e., P[quitting | female]) is $1/3$, the joint probability of quitting and being female can be calculated as: $1/4 \times 1/3 = 1/12$. This table clearly shows that sex and treatment are not independent in Situation 2.

eTable 5. Sufficient and necessary conditions for no confounding in the total population

Confounding in expectation vs. realized confounding	Confounding in distribution vs. confounding in measure	Measure	Sufficient and necessary condition for no confounding in terms of response types [a, b]
Confounding in expectation	Confounding in distribution	NA	$\left\{(r_1+r_2)=\sum_j w_j\left(p_{1j}+p_{2j}\right)\right\}\wedge\left\{(r_1+r_3)=\sum_j w_j\left(q_{1j}+q_{3j}\right)\right\}$ $\Leftrightarrow\left\{\left(p_{1j}+p_{2j}\right)\times P_j[A=1]+\left(q_{1j}+q_{2j}\right)\times P_j[A=0]=\sum_j w_j\left(p_{1j}+p_{2j}\right)\right\}\wedge\left\{\left(p_{1j}+p_{3j}\right)\times P_j[A=1]+\left(q_{1j}+q_{3j}\right)\times P_j[A=0]=\sum_j w_j\left(q_{1j}+q_{3j}\right)\right\}$ (Eq. 6)
Confounding in expectation	Confounding in measure	RD	$(r_1+r_2)-(r_1+r_3)=\sum_j w_j\left(p_{1j}+p_{2j}\right)-\sum_j w_j\left(q_{1j}+q_{3j}\right)\Leftrightarrow\left(p_{2j}-p_{3j}\right)\times P_j[A=1]+\left(q_{2j}-q_{3j}\right)\times P_j[A=0]=\sum_j w_j\left(p_{1j}+p_{2j}\right)-\sum_j w_j\left(q_{1j}+q_{3j}\right)$ (Eq. 7)
Confounding in expectation	Confounding in measure	RR	$\frac{r_1+r_2}{r_1+r_3}=\frac{\sum_j w_j\left(p_{1j}+p_{2j}\right)}{\sum_j w_j\left(q_{1j}+q_{3j}\right)}\Leftrightarrow\frac{\left(p_{1j}+p_{2j}\right)\times P_j[A=1]+\left(q_{1j}+q_{2j}\right)\times P_j[A=0]}{\left(p_{1j}+p_{3j}\right)\times P_j[A=1]+\left(q_{1j}+q_{3j}\right)\times P_j[A=0]}=\frac{\sum_j w_j\left(p_{1j}+p_{2j}\right)}{\sum_j w_j\left(q_{1j}+q_{3j}\right)}$ (Eq. 8)
Realized confounding	Confounding in distribution	NA	$\left\{(r_1+r_2)=\left(p_{1j}+p_{2j}\right)\right\}\wedge\left\{(r_1+r_3)=\left(q_{1j}+q_{3j}\right)\right\}\Leftrightarrow\left\{\left(p_{1j}+p_{2j}\right)=\left(q_{1j}+q_{2j}\right)\right\}\wedge\left\{\left(p_{1j}+p_{3j}\right)=\left(q_{1j}+q_{3j}\right)\right\}$ (Eq. 9)
Realized confounding	Confounding in measure	RD	$(r_1+r_2)-(r_1+r_3)=\left(p_{1j}+p_{2j}\right)-\left(q_{1j}+q_{3j}\right)\Leftrightarrow\left(p_{1j}+p_{3j}\right)\times P_j[A=1]+\left(p_{1j}+p_{2j}\right)\times P_j[A=0]=\left(q_{1j}+q_{3j}\right)\times P_j[A=1]+\left(q_{1j}+q_{2j}\right)\times P_j[A=0]$ (Eq. 10)
Realized confounding	Confounding in measure	RR	$\frac{r_1+r_2}{r_1+r_3}=\frac{p_{1j}+p_{2j}}{q_{1j}+q_{3j}}\Leftrightarrow\left(p_{1j}+p_{2j}\right)\left\{\left(p_{1j}+p_{3j}\right)-\left(q_{1j}+q_{3j}\right)\right\}\times P_j[A=1]=\left(q_{1j}+q_{3j}\right)\left\{\left(q_{1j}+q_{2j}\right)-\left(p_{1j}+p_{2j}\right)\right\}\times P_j[A=0]$ (Eq. 11)

RD, risk difference; RR, risk ratio; NA, not applicable.

We consider exposure as binary A (1 = exposed, 0 = unexposed). We let r_i, i = 1–4 signify a proportion of response type i in the total population (see **Table 2**). We also let p_{ij} and q_{ij} denote proportions of response type i in the exposed group and the unexposed group in scenario #j, respectively; w_j denotes a weight of scenario #j ($\sum_j w_j=1$). Note that r_i can be calculated as: $p_{ij}\times P_j[A=1]+q_{ij}\times P_j[A=0]$, where $P_j[A=a]$ represents the prevalence of A = a in the total population in scenario #j.

[a] The right-hand side of Equation 8 can be expressed as: $\sum_j w_j\left(p_{1j}+p_{2j}\right)\Big/\sum_j w_j\left(q_{1j}+q_{3j}\right)=\left[\sum_j w_j\left(q_{1j}+q_{3j}\right)\left\{\left(p_{1j}+p_{2j}\right)\big/\left(q_{1j}+q_{3j}\right)\right\}\right]\Big/\sum_j w_j\left(q_{1j}+q_{3j}\right)=\sum_j w'_j\left\{\left(p_{1j}+p_{2j}\right)\big/\left(q_{1j}+q_{3j}\right)\right\}$, which is a weighted average of scenario-specific risk ratios, where the weight is $w'_j=w_j\left(q_{1j}+q_{3j}\right)\Big/\sum_k w_k\left(q_{1k}+q_{3k}\right)$ and $\sum_j w'_j=1$. This weight can be interpreted as a proportion of scenario #j to the w_j-weighted average of scenario-specific risks in the unexposed group.

[b] If we apply the conventional definition of bias, sufficient and necessary conditions for unbiasedness of risk difference estimates (i.e., $\left(p_{1j}+p_{2j}\right)-\left(q_{1j}+q_{3j}\right)$) and risk ratio estimates (i.e., $\left(p_{1j}+p_{2j}\right)\big/\left(q_{1j}+q_{3j}\right)$) are described as $(r_1+r_2)-(r_1+r_3)=\sum_j w_j\left\{\left(p_{1j}+p_{2j}\right)-\left(q_{1j}+q_{3j}\right)\right\}$ and $(r_1+r_2)\big/(r_1+r_3)=\sum_j w_j\left\{\left(p_{1j}+p_{2j}\right)\big/\left(q_{1j}+q_{3j}\right)\right\}$, respectively. Note that the former is equivalent to Equation 7, and this is weaker than Equation 6. In contrast, the latter is different from Equation 8, and is neither stronger nor weaker than Equation 6. This point is related to the issue of the unbiased nature of ratio measure estimators.[13]