Appendix 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. **Table 1** and **Table 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:

$$P(x_1, x_2, x_3, x_4) = \frac{\binom{1}{x_1} \binom{1}{x_2} \binom{1}{x_3} \binom{1}{x_4} p_{x_1}^{(1-x_1)} p_{x_2}^{(1-x_2)} p_{x_3}^{(1-x_3)} p_{x_4}^{(1-x_4)}}{\sum_{x_1, x_2, x_3, x_4} \binom{1}{x_1} \binom{1}{x_2} \binom{1}{x_3} \binom{1}{x_4} p_{x_1}^{(1-x_1)} p_{x_2}^{(1-x_2)} p_{x_3}^{(1-x_3)} p_{x_4}^{(1-x_4)}} = \frac{p_{x_1}^{(1-x_1)} p_{x_2}^{(1-x_2)} p_{x_3}^{(1-x_3)} p_{x_4}^{(1-x_4)}}{\sum_{x_1, x_2, x_3, x_4} p_{x_1}^{(1-x_1)} p_{x_2}^{(1-x_2)} p_{x_3}^{(1-x_3)} p_{x_4}^{(1-x_4)}}$$

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 $1/2$. **Table 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:

$$P(x_1, x_2, x_3, x_4) = \frac{\binom{1}{8} \binom{1}{8} \binom{1}{8} \binom{1}{8} p_{x_1}^{(1-x_1)} p_{x_2}^{(1-x_2)} p_{x_3}^{(1-x_3)} p_{x_4}^{(1-x_4)}}{\sum_{x_1, x_2, x_3, x_4} \binom{1}{8} \binom{1}{8} \binom{1}{8} \binom{1}{8} p_{x_1}^{(1-x_1)} p_{x_2}^{(1-x_2)} p_{x_3}^{(1-x_3)} p_{x_4}^{(1-x_4)}} = \frac{1}{6}.$$

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 $1/3$. **Table 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:
\[
P(x_1, x_2, x_3, x_4) = \frac{1}{6} \left( \frac{1}{12} \right)^{x_1} \left( \frac{1}{6} \right)^{x_2} \left( \frac{1}{12} \right)^{x_3} \left( \frac{1}{6} \right)^{x_4} \sum_{x_1, x_2, x_3, x_4} \left( \frac{1}{6} \right)^{x_1} \left( \frac{1}{12} \right)^{x_2} \left( \frac{1}{6} \right)^{x_3} \left( \frac{1}{12} \right)^{x_4} \right)
\]
\[
= \frac{2^{x_1} 2^{x_2} 2^{x_3} 2^{x_4}}{33}.
\]

Consequently, scenario #1 is expected to occur with a probability of \( \frac{16}{33} \); each of the scenarios #2–5 is expected to occur with a probability of \( \frac{4}{33} \); and scenario #6 is expected to occur with a probability of \( \frac{1}{33} \).

**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 \( \theta \) is the parameter of interest and \( E(\hat{\theta}) \) is the expected value of an estimator \( \hat{\theta} \) of the parameter \( \theta \).\(^6,7\) 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”. Note that the above discussion holds true for any measures, although careful consideration is needed when using ratio measures (see the footnote 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.\textsuperscript{9,10} For simplicity, we will generally assume a binary exposure variable (1 = exposed, 0 = unexposed).

According to VanderWeele,\textsuperscript{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 $P(Y_a | C = c) = P(Y | A = a, C = c)$ for all $a$, $c$.

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

We say that there is no *confounding in measure* $\mu$ of the effect of $A$ on $Y$ conditional on $C$ if $\mu(E(Y_i | C = c), E(Y_o | C = c)) = \mu(E(Y | A = 1, C = c), E(Y | A = 0, C = c))$ for all $c$.

To show mathematical definitions of *confounding in expectation* and *realized confounding*, we use $P(Y_a | C = c)$ 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 $P(Y_a | C = c) = E_{J_m} P(Y | A_{J_m} = a, C = c)$ 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 $P(Y_a | C = c) = P(Y | A_j = a, C = c)$ for all $a$, $c$.

An analogous discussion applies when using $\mu(E(Y_i | C = c), E(Y_o | C = c))$ as a measure of interest.
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**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          |

**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        |

**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        |

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        |

Probability of the two males quitting smoking (i.e., $P(\text{quitting} \mid \text{male})$) 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., $P(\text{quitting} \mid \text{female})$) 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.
Table 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      | $\{(r_i + r_j) = \sum w_i (p_{ij} + p_{ij})\} \land \{(r_i + r_j) = \sum w_i (q_{ij} + q_{ij})\}$ |
|                                                   |                                                        |         | $\Rightarrow \{(p_{ij} + p'_{ij}) \times P_{A = 1} + \{(q_{ij} + q'_{ij}) \times P_{A = 0} = \sum w_i (p_{ij} + p_{ij})\} \land \{(p_{ij} + p'_{ij}) \times P_{A = 1} + \{(q_{ij} + q'_{ij}) \times P_{A = 0} = \sum w_i (q_{ij} + q_{ij})\}$ (Eq. 6) |
| Confounding in expectation                         | Confounding in measure                                 | RD      | $(r_i + r_j) - (q_i + q_j) = \sum w_i (p_{ij} + p_{ij}) - \sum w_i (q_{ij} + q_{ij}) \Rightarrow (p_{ij} - p_{ij}) \times P_{A = 1} + \{(q_{ij} - q_{ij}) \times P_{A = 0} = \sum w_i (p_{ij} + p_{ij}) - \sum w_i (q_{ij} + q_{ij})$ (Eq. 7) |
| Confounding in expectation                         | Confounding in measure                                 | RR      | $\frac{\left(r_i + r_j\right) - \sum w_i (p_{ij} + p_{ij}) - \sum w_i (q_{ij} + q_{ij})}{\left(r_i + r_j\right) - \sum w_i (q_{ij} + q_{ij})} \Rightarrow \{(p_{ij} + p_{ij}) \times P_{A = 1} + \{(p_{ij} + p_{ij}) \times P_{A = 0} = \sum w_i (p_{ij} + p_{ij}) - \sum w_i (q_{ij} + q_{ij})$ (Eq. 8) |
| Realized confounding                               | Confounding in distribution                           | NA      | $\{(r_i + r_j) = \sum w_i (p_{ij} + p_{ij})\} \land \{(r_i + r_j) = \sum w_i (q_{ij} + q_{ij})\} \Rightarrow \{(p_{ij} + p_{ij}) = \{(q_{ij} + q_{ij})\}$ (Eq. 9) |
| Realized confounding                               | Confounding in measure                                 | RD      | $(r_i + r_j) - (q_i + q_j) = \{(p_{ij} + p_{ij}) - (q_{ij} + q_{ij}) \Rightarrow (p_{ij} + p_{ij}) \times P_{A = 1} + \{(p_{ij} + p_{ij}) \times P_{A = 0} = \{(q_{ij} + q_{ij}) \times P_{A = 0} = \{(q_{ij} + q_{ij}) \times P_{A = 0} = \{(q_{ij} + q_{ij}) \times P_{A = 0}$ (Eq. 10) |
| Realized confounding                               | Confounding in measure                                 | RR      | $\frac{\left(r_i + r_j\right) - p_{ij} + p_{ij}}{\left(r_i + r_j\right) - q_{ij} + q_{ij}} \Rightarrow \{(p_{ij} + p_{ij})\} = \{(q_{ij} + q_{ij})\} \times P_{A = 1} + \{(q_{ij} + q_{ij})\} \times P_{A = 0} = \{(q_{ij} + q_{ij})\} \times P_{A = 0}$ (Eq. 11) |

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

We consider exposure as binary $A$ (1 = exposed, 0 = unexposed). We let $r_i$ ($i = 1\,\ldots\,4$) 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 $ij$, respectively; $w_i$ denotes a weight of scenario $ij$ ($\sum w_i = 1$). Note that $r_i$ can be calculated as: $p_{ij} \times P_{A = 1} + q_{ij} \times P_{A = 0}$, where $P_{A = a}$ represents the prevalence of $A = a$ in the total population in scenario $ij$.

$^a$ The right-hand side of Equation 8 can be expressed as: $\sum w_i (p_{ij} + p_{ij})/\sum w_i (q_{ij} + q_{ij}) = \left[\sum w_i (q_{ij} + q_{ij})\right] / \left[\sum w_i (q_{ij} + q_{ij})\right]$ which is a weighted average of scenario-specific risk ratios, where the weight is $w_j' = w_j (q_{ij} + q_{ij}) / \sum w_i (q_{ij} + q_{ij})$ and $\sum w_j' = 1$. This weight can be interpreted as a proportion of scenario $ij$ 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., $(p_{ij} + p_{ij}) - (q_{ij} + q_{ij})$) and risk ratio estimates (i.e., $(p_{ij} + p_{ij})/(q_{ij} + q_{ij})$) are described as $(r_i + r_j) = \sum w_i (p_{ij} + p_{ij}) - (q_{ij} + q_{ij})$ and $(r_i + r_j)/(r_i + r_j) = \sum w_i (p_{ij} + p_{ij})/(q_{ij} + q_{ij})$, 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.\textsuperscript{13}