Supplementary information

Graphical comparisons of relative disease burden across multiple risk factors

1 Technical details on the approximations

Again, we first consider the approximations for a binary risk factor, A, and later generalize. Consider a second order Taylor expansion of: $\left(e^{\widehat{\beta_1}} - 1\right)/e^{\widehat{\beta_1}} = 1 - e^{-\widehat{\beta_1}}$ around $\widehat{\beta_1}$ = 0. That is: $1 - e^{-\widehat{\beta_1}} \sim 1 - \left(1 - \widehat{\beta_1} + \widehat{\beta_1^2}/2\right)$ = $\widehat{\beta_1}\left(1 - \widehat{\beta_1}/2\right)$. Plugging this approximation into $(2b)$ yields:

$$\widehat{PAF} \sim \widehat{P(A = 1|Y = 1)}\widehat{\beta_1}\left(1 - \widehat{\beta_1}/2\right). \qquad (S1)$$

(3) is still slightly unwieldly for our purposes; a couple of further steps yields simpler expressions:

(a) For small $\widehat{\beta_1}$, ignoring, we can ignore the second order factor $(S1)$ to derive:

$$\widehat{PAF} \sim \widehat{P(A = 1|Y = 1)}\widehat{\beta_1}. \qquad (S1a)$$

In practice, this first-order approximation may be inacceptably inaccurate, and is not recommended for use. For instance, to achieve an acceptable approximation (perhaps defined as the ratio of $(S1)$ and $(S1a)$) being within 20%), we can solve $\left(1 - \widehat{\beta_1}/2\right) > 0.8$, leading to $\widehat{\beta_1} < 0.4$, implying that this approximation should be used for risk factors with odds ratios less than 1.5.

(b) If $|\widehat{\beta_1}|$ is larger, we may need to keep the quadratic factor in $(S1)$ to obtain an acceptable approximation. To derive an alternative approximation, note that $(S1)$ can be rewritten as $\widehat{PAF} \sim \widehat{\beta_1}F$ wher $F = \widehat{P(A = 1|Y = 1)}\left(1 - \widehat{\beta_1}/2\right)$

It follows that:

$$F = \widehat{P(A = 1|Y = 0)}\frac{\widehat{P(A = 1|Y = 1)}}{\widehat{P(A = 1|Y = 0)}}\left(1 - \widehat{\beta_1}/2\right)$$

$$= \widehat{P(A = 1|Y = 0)}\frac{\widehat{P(Y = 1|A = 1)}/\widehat{P(Y = 1)}}{\widehat{P(Y = 0|A = 1)}/\widehat{P(Y = 0)}}\left(1 - \widehat{\beta_1}/2\right)$$

$$\sim \widehat{P(A = 1|Y = 0)}\frac{\widehat{P(Y = 1|A = 1)}}{\widehat{P(Y = 1)}}\left(1 - \widehat{\beta_1}/2\right),$$

with the equality in line 2 following by Bayes theorem and the final approximation by the rare disease assumption.

Now if $\widehat{\beta_1} > 0$, we would expect that $\widehat{P(Y=1|A=1)}/\widehat{P(Y=1)} > 1$ (provided confounding isn't reversing the conditional and unconditional directions of association), and for the same reason when $\widehat{\beta_1} < 0$ it is likely that $\widehat{P(Y=1|A=1)}/\widehat{P(Y=1)} < 1$. Under the scenario that the 2nd and 3rd terms in (3) are approximate reciprocals:

$$\frac{\widehat{P(Y=1|A=1)}}{\widehat{P(Y=1)}}\left(1-\widehat{\beta_1}/2\right)\sim 1 \tag{S1b}$$

and the two-term expansion given in (3) can be approximated by (3c):

$$\widehat{PAF}\sim \widehat{P(A=1|Y=0)}\widehat{\beta_1}. \tag{S1c}$$

That is, an approximation for the population attributable fraction is the prevalence of the exposure in controls multiplied by the log-odds ratio of the association.
As (S1c) may approximate the 2nd order Taylor expansion, it will usually be more accurate than (S1a), which is the first order approximation. See section 2 for a justification of when this might be most accurate.

Approximations for multicategory and continuous exposures.

The previous approximations extend easily to multicategory exposures. Suppose that the exposure A can take $K+1$ values: $a \in 0,1,\dots,K$ with $a=0$, a reference level such that:

$$P\left(Y^{a=j}=1\right) \geq P(Y^{a=0}=1) \tag{S2}$$

for all j. Under the assumptions that (a) adjusting for the set of variables, $\mathbf{C}$, is sufficient to eliminate confounding of the exposure/outcome relationship, that is $Y^{a=j}$, that is $A \perp Y^{a=j}|C$ for all j (b) that the relative risk $P\left(Y^{a=j}=1|C=c\right)/P(Y^{a=0}=1|C=c) = P(Y=1|A=j, C=c)/P(Y=1|A=0,C=c) = RR_j$ is independent of c for all j, (1) can be re-expressed as:

$$PAF = \sum_{j=1}^{K} P(A=j|Y=1)\left(RR_j-1\right)/RR_j\,. \tag{S3}$$

Under the rare disease assumption, the absence of an interaction (between A and C) suggests that the conditional association between Y and A given c should be modelled via logistic regression:

$$\text{logit}\left(P(Y=1|\,A=j, C=c)\right) = \beta_0 + \beta_j + f(c),$$

for j ≥ 1. (9) can then be estimated as:

$$\widehat{\mathrm{PAF}} = \sum_{j=1}^{K} \mathrm{P}(\mathrm{A}=\mathrm{j}|\mathrm{Y}=1)\left(e^{\widehat{\beta_j}}-1\right)/e^{\widehat{\beta_j}}. \qquad (S4)$$

Assuming 'small' β_j, $j \leq K$, each term in (S4) can in turn be approximated via Taylor expansion as before (when deriving (S1c)):

$$\widehat{\mathrm{PAF}} \sim \sum_{j=1}^{K} \mathrm{P}(\widehat{\mathrm{A}=\mathrm{j}|\mathrm{Y}}=0)\widehat{\beta_j} \qquad (S5)$$

Finally, consider a continuous exposure, A, taking any possible value on the real line. Suppose that j_0 is a minimum risk level of the exposure such that:

$$\mathrm{P}\left(\mathrm{Y}^{a=j}=1\right) \geq \mathrm{P}\left(\mathrm{Y}^{a=j_0}=1\right) \qquad (S6)$$

In this case, assuming again no interaction between the exposure, A and C on the relative risk scale, and that adjustment for C is sufficient to eliminate confounding, we can re-express $(E5)$ from the main manuscript as

$$\mathrm{PAF} = \int_{-\infty}^{\infty} f(j|1)\frac{\mathrm{RR}(j)-1}{\mathrm{RR}(j)}\,dj, \qquad (S7)$$

where $\mathrm{P}\left(\mathrm{Y}^{a=j}=1|\mathrm{C}=c\right)/\mathrm{P}\left(\mathrm{Y}^{a=j_0}=1|\mathrm{C}=c\right)=\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=j,\mathrm{C}=c)/\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=j_0,\mathrm{C}=c)=\mathrm{RR}(j)$. We assume again an additive model relating the response to exposure and possible confounders,C:

$$\mathrm{logit}\left(\mathrm{P}(\mathrm{Y}=1|\ \mathrm{A}=j,\mathrm{C}=c)\right)=\beta_{j_0}+\beta(j)\ +f(c), \qquad (S8)$$

where $\beta(j)$ is a continuous positive function on the real line satisfying $\beta(j_0)=0$.

The same approximations work again, except that the sums in $(S5)$ now turns into an integral:

$$\widehat{\mathrm{PAF}} \sim \int_{-\infty}^{\infty} \widehat{f(j|0)}\widehat{\beta(j)}\,dj, \qquad (S9)$$

where $\widehat{f(j|0)}$ is a estimated density functions (with respect to Lebesgue measure) for A in controls (i.e. when $Y=0$).

2 When is the approximation most accurate?

The approximation $(\mathrm{S1b})$:

$$\frac{\widehat{\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=1)}}{\widehat{\mathrm{P}(\mathrm{Y}=1)}}\left(1-\widehat{\beta_1}/2\right)\sim 1 \tag{S1b}$$

was used to justify $(\mathrm{S1c})$, which is the approximation used in the plots. This suggests that the error of approximating the second order Taylor expansion $\widehat{\mathrm{P}(\mathrm{A}=1|\mathrm{Y}=1)}\widehat{\beta_1}\left(1-\widehat{\beta_1}/2\right)$ with $\widehat{\mathrm{PAF}}\sim\widehat{\mathrm{P}(\mathrm{A}=1|\mathrm{Y}=0)}\widehat{\beta_1}$ should be minimal when

$$\frac{\widehat{\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=1)}}{\widehat{\mathrm{P}(\mathrm{Y}=1)}}=\left(1-\widehat{\beta_1}/2\right)^{-1} \tag{S10}$$

When is $(\mathrm{S10})$ approximately true? Well, the left hand side (LHS) can be re-expressed as:

$$\mathrm{LHS}=\left(\frac{\widehat{\mathrm{P}(\mathrm{A}=1)}\widehat{\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=1)}+\widehat{\mathrm{P}(\mathrm{A}=0)}\widehat{\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=0)}}{\widehat{\mathrm{P}(\mathrm{Y}=1|\mathrm{A}=1)}}\right)^{-1}$$

$$=\left(\widehat{\mathrm{P}(\mathrm{A}=1)}+\widehat{\mathrm{RR}}^{-1}\widehat{\mathrm{P}(\mathrm{A}=0)}\right)^{-1}=\frac{\widehat{\mathrm{RR}}}{\widehat{\mathrm{RR}}\widehat{\mathrm{P}(\mathrm{A}=1)}+\widehat{\mathrm{P}(\mathrm{A}=0)}}$$

$$\sim\frac{\mathrm{e}^{\widehat{\beta}}}{\mathrm{e}^{\widehat{\beta}}\widehat{\mathrm{P}(\mathrm{A}=1)}+\widehat{\mathrm{P}(\mathrm{A}=0)}}$$

$$\sim\frac{1+\widehat{\beta}}{\left(1+\widehat{\beta}\right)\widehat{\mathrm{P}(\mathrm{A}=1)}+\widehat{\mathrm{P}(\mathrm{A}=0)}}$$

the last approximation via a first order Taylor approximation of $\mathrm{e}^{\widehat{\beta}}$ around $\widehat{\beta}=0$

Where as the RHS is:

$$\mathrm{RHS}\;=\;\left(1-\widehat{\beta_1}/2\right)^{-1}\sim 1+\beta/2$$

again via a first order Taylor approximation of $\left(1-\widehat{\beta_1}/2\right)^{-1}$around $\widehat{\beta}=0$.

Equating the right and left sides we get:

$$\frac{1+\widehat{\beta}}{\left(1+\widehat{\beta}\right)\widehat{\mathrm{P}(\mathrm{A}=1)}+\widehat{\mathrm{P}(\mathrm{A}=0)}}=1+\beta/2$$

which will be approximately true if $\widehat{P(A=1)} \sim \widehat{P(A=1|Y=0)} = 0.5$. That the approximation works best (in terms of ratio-bias) when the prevalence of the risk factor is roughly 0.5 is shown numerically in the Figure 3.

3 Proof of equivalence of (1) and (2) in the main manuscript.

Assume a continuous covariate C with possible values in the real line, and density f(c) with respect to Lebesgue measure. The argument below can be generalized for multidimensional C mixing both discrete and continuous variables by replacing the integrals with a mixture of integrals and summations over the respective ranges of the measured covariates.

$$\mathrm{PAF} = \frac{P(Y=1) - P(Y^{a=0}=1)}{P(Y=1)}$$

$$\frac{E(E(Y|A,C)) - E(E(Y^{a=0}|A,C))}{P(Y=1)}$$

$$= \frac{\sum_{a\in 0,1} \int P(Y=1|A=a,C=c) - P(Y^{a=0}=1|A=a,C=c)\, f(c)P(A=a|C=c)dc}{P(Y=1)}$$

Note that the conditional exchangeability condition is that $Y^{a=0}$ and A are independent given the covariates c. This implies that $P(Y^{a=0}=1|A=a,C=c) = P(Y^{a=0}=1|A=0,C=c)$. Noting that $Y = Y^{a=0}$ when A=0, it follows that $P(Y^{a=0}=1|A=0,C=c) = P(Y=1|A=0,C=c)$. Plugging this into the above:

$$= \frac{\sum_{a\in 0,1} \int (P(Y=1|A=a,C=c) - P(Y=1|A=0,C=c))\, P(A=a|C=c)f(c)dc}{P(Y=1)}$$

$$= \frac{\int (P(Y=1|A=1,C=c) - P(Y=1|A=0,C=c))\, P(A=1|C=c)f(c)dc}{P(Y=1)}$$

$$= \frac{\int (1-RR^{-1})(P(Y=1|A=1,C=c)\, P(A=1|C=c)f(c)dc}{P(Y=1)}$$

$$= (1-RR^{-1})\frac{\int (P(Y=1,A=1|C=c)f(c)dc}{P(Y=1)}$$

$$= (1-RR^{-1})\frac{P(A=1,Y=1)}{P(Y=1)}$$

$$= (1-RR^{-1})P(A=1|Y=1)$$