graphPAF: An R package to estimate and display population attributable fractions

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Abstract

graphPAF is a comprehensive package designed for estimation, inference and display of population attributable fractions (PAF)s and impact fractions. In addition to allowing inference for standard PAFs and impact fractions, **graphPAF** facilitates display of PAFs over multiple risk factors using fan plots and nomograms, calculations of PAFs for continuous exposures, inference for PAFs appropriate for specific risk-factor → mediator → outcome pathways (pathway-specific PAFs) and Bayesian network based calculations and inference for joint, sequential and average PAFs in scenarios where multiple risk factors are of interest. In summary, **graphPAF** extends and consolidates existing packages for PAF estimation in multiple ways. This vignette serves as a broad overview of theory and estimation approaches appropriate for attributable fractions, as well as a guide regarding how to use the **graphPAF** package in practice.

Keywords: PAF, Bayesian network, causal inference, mediation, epidemiology, nomogram.

1. Introduction

Population attributable fractions (PAFs) measure extent to which disease burden, for example the level of heart disease or cancer, in some population is related to a particular behaviour or exposure. Often these behaviours and exposures are referred to as risk factors, with typically examples being smoking, inactivity and air pollution. The most straightforward examples of PAFs pertain to risk factors that can be eliminated from the population, at least in theory. For instance, one could imagine a population similar to Ireland in almost every way (for instance having similar demographics, culture, a similar health system and so on), except that nobody in this population smoked. How might the rate of heart failure in hypothetical nonsmoking Ireland compare to the rate in real Ireland? If the PAF for heart disease attributable for smoking is 12% (as was estimated in Sinha, Ning, Carnethon, Allen, Wilkins, Lloyd-Jones, and Khan (2021)), this means that 12% of the cases of heart failure that occur in the real Ireland, would be avoided in a hypothetical Ireland where nobody smoked. PAFs are important metrics for determining how pertinent particular risk factors are in determining disease, as well as ranking differing risk factors as targets for health interventions.

There are a number of currently available *R* packages for estimating PAFs under various study designs, mostly designed for the standard setting that considers population level elimination of a single binary valued risk factor. `paf` implements methods described in Chen, Lin, and Zeng (2010) and concentrates on estimation under cohort designs using a Proportional Hazards

model. `attribrisk` Schenck, Atkinson, Crowson, and Therneau (2014) estimates PAFs in matched and unmatched case-control designs. More recently, `AF` and `stdReg` described in Dahlqwist, Zetterqvist, Pawitan, and Sjölander (2016) and Sjölander (2018) enable estimation of PAFs in cross sectional, case-control and cohort settings. `pifpaf` Camacho-García-Formentí and Zepeda-Tello (2019) specialises on estimation of PAFs using cross sectional summary data over several independent populations. The new *R* package `graphPAF` described here also estimates PAFs for cross sectional, case-control and cohort study designs under random samples. Unlike some of the aforementioned packages, `graphPAF` also can estimate PAFs for multilevel risk factors and under survey data collection schemes. It also enables PAF calculations in more complicated settings as we describe below.

In the case that many risk factors are under consideration, differing kinds of analyses may be of interest. `graphPAF` implements fan plots and nomograms that graphically display the interrelationships between PAFs, relative risk and risk factor prevalence for multiple risk factors, as described in Ferguson, O'Leary, Maturo, Yusuf, and O'Donnell (2019). These visualisations can be useful to identify clusters of risk factors that behave similarly, to visually compare attributable disease burden due to differing risk factors, and sometimes to visualise the effects of interventions.

Joint PAFs refer to collective disease burden represented by a group of risk factors (and involves consideration of a hypothetical population where all risk factors in the group were eliminated). Sequential PAFs examine incremental effects on population disease prevalence when each of the risk factors in the group is eliminated according to some order. Average PAFs (literally an average of all possible sequential PAFs for each risk factor), allow one to partition the joint PAF into contributions for each risk factor. Previous *R* implementations of average, sequential and joint PAFs (for example the *R* package `averisk`, Ferguson, Alvarez-Iglesias, Newell, Hinde, and O'Donnell (2018)), have been agnostic to the causal structure linking risk factors to disease, which can result in biased estimation in scenarios where multiple risk factors of interest are on the same causal pathway to disease (for instance if smoking affects blood pressure which affects disease, smoking and blood pressure would be considered to be on the same causal pathway). In contrast, in these settings `graphPAF` incorporates known risk factor/risk factor and risk factor/disease relationships using a causal Bayesian network model Ferguson, O'Connell, and O'Donnell (2020b) and as a result can alleviate these biases.

Referring to the putative pathway: 'smoking → blood pressure → heart disease' mentioned above, one might wonder about the extent to which this particular pathway contributes to heart disease. This is measured by the pathway-specific PAF O'Connell and Ferguson (2022) which can also be calculated by `graphPAF`. Moreover, smoking may affect heart disease through other mechanisms; for instance, through effects on blood cholesterol. Provided data is available, pathway-specific PAFs can be estimated for these alternative pathways which may help to determine the most important mechanisms through which the risk factor of interest leads to disease.

In the case of continuous risk factors or exposures, zero exposure or alternatively elimination of the risk factor can be nonsensical to consider. Consider body mass index (BMI) as an example: zero BMI is obviously unattainable and extremely low BMI might be as detrimental to one's health as high BMI. Versions of PAFs appropriate in these settings, that allow valid comparisons of disease burden across differing exposures and don't resort to categorisation, are described in Ferguson, Maturo, Yusuf, and O'Donnell (2020a). These metrics are also implemented in `graphPAF`.

In summary, `graphPAF` extends and consolidates existing packages for PAF estimation in multiple ways. In this manuscript, we describe its features in more depth, interweaving between the theory for PAF estimation and using `graphPAF` in practice.

2. Basic PAF estimation

In this section, we imagine a setting where the risk factor is either binary, or perhaps multi-category, with some level indicating 'elimination' for the risk factor. Let Y denote a binary disease outcome (1 indicating disease) for a randomly selected individual from the population, and Y_0 the same binary disease outcome but where the individual is sampled from a hypothetical population with the risk factor eliminated. The PAF can be defined as:

$$PAF = \frac{P(Y=1) - P(Y_0=1)}{P(Y=1)} \tag{1}$$

where $P(Y=1)$ represents the prevalence of disease in the current population and $P(Y_0=1)$ the prevalence of disease in the hypothetical population with the risk factor eliminated. (1) is an appropriate estimand in case-control and cross sectional studies. Often in longitudinal cohort studies, a cohort of healthy individuals are followed over time with some eventually developing disease. In this setting, a differing kind of PAF is calculated where the cumulative incidence of disease for that cohort as a function of time is compared to what the incidence would be if the factor had been eliminated from the cohort:

$$PAF(t) = \frac{P(T \leq t) - P(T_0 \leq t)}{P(T \leq t)}. \tag{2}$$

Here random sampling is interpreted as random sampling from the cohort of interest and PAF, Y and Y_0 from (1) are replaced by $PAF(t)$, $I\{T \leq t\}$ and $I\{T_0 \leq t\}$, with the random variables T and T_0 representing time to disease in the current population and under hypothetical elimination of the risk factor. In the setting of competing events (such as death) we can define T as the time an individual would have developed disease had the competing event not occurred, and the PAF in terms of prevented disease under elimination of the risk factor provided the competing event did not happen. It should be noted that (2) can only be estimated in the presence of competing events under limited conditions, such as under the assumption that censoring of the true survival time T by the competing event is non-informative. We can also incorporate competing events directly in the definition of the PAF. Suppose Δ represents an indicator for the event that happens first with $\Delta = 1$ indicating that disease occurred before any other event. We can then write

$$PAF^*(t) = \frac{P(T \leq t \text{ and } \Delta = 1) - P(T_0 \leq t \text{ and } \Delta_0 = 1)}{P(T \leq t \text{ and } \Delta = 1)}. \tag{3}$$

Note that as $t \to \infty$, $PAF^*(t)$ converges to (4) below:

$$PAF^* = \frac{P(\Delta = 1) - P(\Delta_0 = 1)}{P(\Delta = 1)} \tag{4}$$

which is essentially the PAF for future disease incidence in the cohort, as described by Laaksonen, Härkänen, Knekt, Virtala, and Oja (2010). While (3) may at first seem a more sensible

estimand than (2) in the presence of competing events, care must be taken in its interpretation. For instance, if the risk factor leads to early mortality due to other mechanisms than the disease of interest (3) may be negative for large t even when the risk factor causes disease. In other words, while (3) is the proportional difference in cumulative incidence in disease by time t due to removing the risk factor, it can't be interpreted as disease incidence prevented by eliminating the risk factor. In contrast (2) does have an interpretation in terms of prevented hypothetical incidence in the absence of competing events.

Note that (1), (2) and (3) are causal entities, and unbiased estimation with observational data requires relatively strong assumptions. For instance, if the random variable $A \in \{0, 1, ..., n_A\}$ represents the observed risk factor ($A = 0$ coding for elimination), one cannot say that $P(Y = 1 \mid A = 0) = P(Y_0 = 1)$ unless the risk factor A could be considered randomly assigned. Informal sufficient conditions for the possibility of asymptotically unbiased estimation of (1) are:

1. Unambiguous definition of the potential outcome: Y_0, representing risk factor elimination. (This is essentially the famous stable unit treated value assumption (SUTVA), first described in Rubin (1974))

2. The measurement of a collection of covariates C, so that for any observed value of C, $P(Y = 1 \mid A = 0, C) = P(Y_0 = 1 \mid C)$. This will be true if within joint strata of the covariates C, the risk factor A behaves as if it were randomly assigned. The collection C is sometimes referred to as a sufficient adjustment set of covariates.

3. Any proposed model for disease probability conditional on risk factor and covariates that is used in the subsequent PAF estimator is correctly specified. In other words, if we use an estimator $\hat{P}(Y_i = 1 \mid A_i, C_i)$ of $P(Y = 1 \mid A = 0, C)$ based on an assumed parametric statistical model, correct functional relationships and interactions between A, C and the probability of disease need to be specified in the model.

Similar conditions need to be assumed to estimate (2) and (3). The variables C are often, but not always, a set of confounders of the risk factor/outcome relationship (that is they are joint causes of A and Y). We will assume the veracity of these conditions (including the measurement of a sufficient adjustment set C) in what follows, although their validity should be carefully considered in any practical application.

Assuming these conditions, differing estimators are appropriate dependent on the study design. For cross sectional and case-control designs, (1) can be estimated by

$$\hat{PAF} = \frac{\sum_{i \leq N} w_i (\hat{P}(Y_i = 1 \mid A_i, C_i) - \hat{P}(Y_i = 1 \mid A_i = 0, C_i))}{\sum_{i \leq N} w_i \hat{P}(Y_i = 1 \mid A_i, C_i)} \tag{5}$$

where $i \in \{1, ..., N\}$ indexes the sampled individuals, Y_i, A_i, C_i the disease outcome, risk factor and covariates for individual i, and w_i is a weight specific to individual i. Usually w_i would be set to 1 for cross sectional datasets and is specified based on disease prevalence for case-control datasets. In `graphPAF`, $\hat{P}(Y_i = 1 \mid A_i, C_i)$ may be estimated via log linear, logistic or conditional logistic models, with estimation using conditional logistic models only possible when disease prevalence is known. Note that when disease prevalence is specified as π, `graphPAF` adjusts predicted probabilities via adding a constant to the linear predictor of the estimated model to ensure that $\sum_{i \leq N} \hat{P}(Y_i = 1 \mid A_i, C_i) = N\pi$. As an example, for a

logistic model with a single univariate confounder, C, with assumed regression coefficients, β_0, β_1 and β_2, for the intercept, A and C, this entails finding the constant, c, such that: $\sum_{i\leq N} \frac{e^{c+\hat{\beta}_0+\hat{\beta}_1 A+\hat{\beta}_2 C}}{1+e^{c+\hat{\beta}_0+\hat{\beta}_1 A+\hat{\beta}_2 C}} = N\pi$, and then substituting modified predicted probabilities: $\hat{P}(Y_i = 1 \mid A_i, C_i) = \sum_{i\leq N} \frac{e^{c+\hat{\beta}_0+\hat{\beta}_1 A+\hat{\beta}_2 C}}{1+e^{c+\hat{\beta}_0+\hat{\beta}_1 A+\hat{\beta}_2 C}}$ into (5). In addition, separate weights for disease cases and controls are computed so that the empirical weighted prevalence of disease: $\frac{\sum w_i Y_i}{\sum w_i} = \pi$. If disease prevalence is unknown, (5) can't be used for estimation in case-control studies; instead, the formula by Bruzzi, Green, Byar, Brinton, and Schairer (1985) should be used:

$$\hat{PAF} = 1 - \frac{1}{N_c} \sum_{i\leq N:Y_i=1} \frac{\hat{P}(Y = 1 \mid A_i = 0, C_i)}{\hat{P}(Y = 1 \mid A_i, C_i)} = 1 - \frac{1}{N_c} \sum_{i\leq N:Y_i=1} \hat{RR}_i{}^{-1} \tag{6}$$

where $\hat{RR}_i = P(Y = 1 \mid A_i, C_i)/P(Y = 1 \mid A_i = 0, C_i)$ is the estimated relative increase in disease risk encountered by individual i based on their risk factor value A_i and $N_c = \sum_{i\leq N} I\{Y_i = 1\}$ is the number of cases in the data set. $\hat{RR}_i$ can be approximated by the correspondingly estimated odds ratio in case-control study designs provided the disease is relatively rare.

In cohort designs, often Cox Proportional Hazard models are used to estimate (2). Under the proportional hazards assumption, suppose $\hat{r}(C_i, A_i)$ is the estimated hazard ratio for an individual with covariates C_i and risk factor A_i compared to their hazard assuming all covariates and risk factors were at reference levels (defined as 0 for continuous covariates). Let $\hat{H}_0(t)$ be an estimate of the cumulative baseline hazard function (`graphPAF` uses the Kalbfleich Prentice estimate). $PAF(t)$ is then estimated as

$$\hat{PAF}(t) = \frac{\sum_{i\leq N} e^{-\hat{H}_0(t)\hat{r}(C_i,A_i=0)} - e^{-\hat{H}_0(t)\hat{r}(C_i,A_i)}}{\sum_{i\leq N}(1 - e^{-\hat{H}_0(t)\hat{r}(C_i,A_i)})}. \tag{7}$$

To estimate $PAF^*(t)$, $\hat{r}(C_i, A_i)$ can be replaced in (7) by the estimated Fine Gray subdistribution hazard ratio: $\hat{r}^{FG}(C_i, A_i)$ for disease incidence, and $e^{-\hat{H}_0(t)}$ by $e^{-\int_0^t \hat{h}_0^{FG}(u)du}$, where $\hat{h}_0^{FG}(u)$ is the estimated baseline subdistribution hazard function at time u. These functions can be estimated by prior weighting of the Cox model, as will be described in Section 2.1.

2.1. Estimation of PAF in cross sectional and case-control designs

The function `PAF_calc_discrete` facilitates PAF estimation for binary and multilevel risk factors for cross sectional, case-control and longitudinal cohort designs. As an example, consider estimating the PAF for the variable `exercise`, a binary indicator for physical inactivity, using the dataframe `stroke_reduced`, included in `graphPAF`. `stroke_reduced` is a simulated matched case-control dataset including 10 stroke risk factors (with R variable names: `smoking`, `stress`, `waist_hip_ratio`, `exercise`, `alcohol`, `diabetes`, `early_stage_heart_disease`, `diet`, `lipids`, `education`, `high_blood_pressure`) for 6,856 stroke cases and 6,856 stroke controls. Stroke cases, as indicated by the variable `case=1`, were matched with controls on the variables `age` (in 5 year windows), `gender` and `region`. The simulated data were generated using probability distributions estimated using a Bayesian network model fitted to real data from the INTERSTROKE project O'Donnell, Chin, Sumathy, and et al (2016). In INTER-

STROKE, the stroke cases represented first occurrences of stroke, and we will presume the same true for the simulated data, `stroke_reduced`.

To deal with the case-control matching, we first fit a conditional logistic model to describe the relationships between the prevalence of stroke, exercise and assumed confounders, with the following commands:

```
> library(splines)
> library(survival)
> library(graphPAF)
> model_exercise <- clogit(formula = case ~ age
   + education +exercise + ns(diet, df = 3) + smoking + alcohol
    + stress + ns(lipids,df = 3) + ns(waist_hip_ratio, df = 3)
    + high_blood_pressure +strata(strata),data=stroke_reduced)
```

The function for PAF estimation with a binary (or multilevel) risk factor in `graphPAF` is `PAF_calc_discrete`. A minimum of 4 arguments need to be specified to use this function: `model`, a fitted statistical model (either a `glm`, with log or logit link, a conditional logistic regression fitted with `clogit` or a proportional hazards regression fitted with `coxph`), a character string, `riskfactor` indicating the variable name of the riskfactor, a character, `refval`, indicating the reference level of the risk factor and the dataframe, `data`, that was used to fit the statistical model. Specifiying these arguments, `PAF_calc_discrete` returns an estimated PAF of 33% for inactivity:

```
> PAF_calc_discrete(model=model_exercise, riskfactor="exercise",
 refval=0, data=stroke_reduced)
```

```
0.3322625
```

For case-control datasets such as `stroke_reduced` the 'Bruzzi' method Bruzzi *et al.* (1985) which avoids the necessity of specifying disease prevalence is recommended. This is the default approach employed by `PAF_calc_discrete` as well as in other `graphPAF` functions such as `PAF_calc_continuous` and `impact_fraction`. However, the 'Bruzzi' approach requires approximating relative risks with odds ratios which will generate substantial inaccuracy for common diseases. If prevalence or average incidence of the disease over a period of time is known, the 'direct' method can be used as an alternative by utilising the extra arguments `calculation_method="D"` and `prev`. The average global yearly incidence of first stroke estimated by Anonymous (2018) was approximately 0.0035. This indicates that using `prev=0.0035` in `PAF_calc_discrete` will estimate $PAF(1)$, that is equation (2) at $t = 1$:

```
> PAF_calc_discrete(model_exercise, "exercise", 0,
stroke_reduced,calculation_method="D", prev=0.0035)
```

```
0.3196773
```

If disease prevalence (rather than an estimated incidence) is available and used in the argument `prev`, the estimator will estimate equation (1). Note that when lifetime disease incidence across the cohort is low, relative risks and hazard ratios should roughly correspond and one would expect (1) to be approximately equal to (2) at varying t.

For PAF calculations with cross sectional data, a `glm` model (with a logistic or log-linear link) should first be fit that describes the relationship between risk factor and disease, conditional on covariates. Provided the sample is representative of the source population, the argument `prev` doesn't need to be set, and `calculation_method="D"` should instead be used. `PAF_calc_discrete` will then estimate equation (1).

Bootstrap-calculated confidence intervals for PAF can be requested via `ci=TRUE`. The bootstrap is assisted by the R package `boot` Canty and Ripley (2022) which is loaded by default when `graphPAF` is installed. Parallelisation over multiple CPU cores is available by setting the option `boot.ncpus` to an integer above 1 prior to estimation of the PAF. The number of bootstrap replications can be changed using the argument `boot_rep`, and the confidence level via the argument `ci_level`. Similar bootstrap generated confidence intervals (requested using the same arguments) are also available for other `graphPAF` functions detailed later such as: `impact_fraction`,`PAF_calc_continuous`,`ps_paf`,`joint_paf`,`average_paf` and `seq_paf`. Note the R defaults for these arguments: `ci=FALSE`,`boot_rep=50` and `ci_level=0.95`. In the code snippets that follow (and in later parts of the manuscript), we will set `ci=TRUE` when confidence intervals are required with the understanding that the number of Bootstrap iterates is 50 and the confidence level is 95%. The confidence intervals calculated by default are bias-corrected symmetric intervals that effectively assume the PAF estimator to be normally distributed. This can be changed by altering the argument `ci_type` to either `basic`, `perc` or `bca` (note that using `perc` and `bca` necessitates a larger number of bootstrap iterates for accuracy). Bootstrap intervals will vary slightly over differing executions with differing starting random number seeds, as stored in the variable `.Random.seed`. See the documentation for the `boot` library for more details. Canty and Ripley (2022).

```
>library(parallel)
>options(boot.ncpus=5) # set to number of cores on machine
>PAF_calc_discrete(model_exercise, "exercise", refval=0, data=stroke_reduced,
ci=TRUE)
```

est	bias	debiased_est	norm_lower	norm_upper
0.33200	0.00547	0.32700	0.26000	0.39300

`PAF_calc_discrete` can also estimate the PAF in cohort datasets using equation (7) if a fitted cox proportional hazard model object (that is an object of class `coxph`) is supplied to the function. For example, in the dataframe `stroke_reduced`, `time` denotes a simulated survival time to some event in the stroke controls, where individuals with `event=0` are considered to not have experienced the event at study completion or when they left the study. The following model might be fit:

```
> model_high_blood_pressure_coxph <- coxph(formula = Surv(time,event) ~
    ns(age,df=5) + education + exercise + ns(diet, df = 3) + smoking +
      alcohol + stress + ns(lipids,df = 3) + ns(waist_hip_ratio, df = 3)
    + high_blood_pressure,data=stroke_reduced[stroke_reduced$case==0,])
```

We can use `PAF_calc_discrete` to estimate the proportion of the events in the subcohort that might have been avoided in various time periods if nobody was hypertensive, hypertension being represented by the binary variable `high_blood_pressure`. For survival data, we must use `calculation_method="D"` (the argument `prev` should not be specified). At time 0 nobody had experienced an event, and over time the cumulative number of events (and also the proportion of events that might be avoided) changes. The user can specify the times, t, at which to calculate $PAF(t)$ using the argument `t_vector`:

```
PAF_calc_discrete(model_high_blood_pressure_coxph,"high_blood_pressure",
 refval=0, data = stroke_reduced[stroke_reduced$case==0,],
 calculation_method="D", ci=TRUE, t_vector=c(1,2,3,4,5,6,7,8,9))
```

```
    est    bias debiased_est norm_lower norm_upper
1 0.397 0.00341        0.394     0.3640      0.424
2 0.391 0.00317        0.388     0.3590      0.417
3 0.379 0.00369        0.376     0.3450      0.406
4 0.361 0.00402        0.357     0.3210      0.393
5 0.327 0.00483        0.322     0.2740      0.370
6 0.293 0.00585        0.287     0.2270      0.347
7 0.256 0.00653        0.249     0.1800      0.319
8 0.220 0.00804        0.212     0.1350      0.288
9 0.176 0.00869        0.168     0.0876      0.248
```

The results indicate that while 39.7% of events that happen with a year might have been avoided in a hypertension-free population, only 17.6% of events that happen within 9 years would be avoided. This is the typical pattern one expects for an event such as death which (unfortunately) can only be delayed but not prevented by the risk factor's absence.

If data on competing events exists (3) may be estimated instead of (2). The first step is to fit a weighted Cox model with weights calculated using the function `finegray` from the `survival` package. Sending the weighted cox model to `PAF_calc_discrete` will utilise the Fine Gray modification of (7) described earlier. See Therneau, Crowson, and Atkinson (2021) for more details.

2.2. Estimation of PAFs for data collected from surveys

Equation (4) and weighted versions of equation (5) and (6) can also used to calculate attributable estimates for data collected on surveys. This can be implemented through `graphPAF` by using the argument `weight_vec` in the `PAF_calc_discrete` function, where `weight_vec` is a vector of survey weights. A regression model (`glm` or `coxph`) estimated with weighted

maximum likelihood with the same weights should be given as the `model` argument in this case. Note that confidence intervals will be calculated using standard bootstrap techniques (including bootstraping `weight_vec`) and may give incorrect results, particularly for surveys involving cluster sampling. One workaround would be for a user to use `graphPAF` as a tool to generate point estimates, but design their own custom resampling regime that replicates the population sampling scheme used in the survey, and bootstrap according to this custom sampling scheme. See Heeringa, Berglund, West, Mellipilán, and Portier (2015) for more details regarding estimating PAF estimation with survey data.

2.3. Estimation of Impact fractions

While PAFs can summarise the overall impact or importance of a risk factor on disease burden, they tend to give an overly optimistic impression of what an intervention on that risk factor might achieve. The predominant reasons for this are first that it may be difficult if not impossible to eliminate the risk factor from the population (think of the difficulties in preventing all forms of smoking or alcohol use or enticing an entire population to change their dietary habits) and second that even if one could eliminate the risk factor, the risk of disease in individuals who previously were exposed might not equal the disease risk if they were never exposed (for instance, former smokers may have higher disease risk than comparable individuals who never smoked) Bulterys, Morgenstern, and Weed (1997).

In contrast, population impact fractions purport to measure the proportional reduction in disease risk from a realistic health intervention that may reduce the prevalence of a risk factor (rather than eliminate the risk factor), or perhaps favorably change the collective statistical distribution of many risk factors. The function `impact_fraction` in `graphPAF` can estimate impact fractions under the study designs considered above (cross sectional, cohort and case-control). We first need to specify how the health intervention changes the distribution of risk factors that might affect disease, through the `new_data` argument. For instance, imagine a health intervention (perhaps a national campaign to encourage walking) reduces the prevalence of inactivity by 20%. Assuming the intervention has no effect on any other risk factor, the following code shows how such an intervention might be specified using the `new_data` argument

```
> new_data <- stroke_reduced
> N <- nrow(new_data)
> inactive_patients <- (1:N)[stroke_reduced$exercise==1]
> N_inactive <- sum(stroke_reduced$exercise)
> newly_active_patients <- inactive_patients[sample(1:N_inactive,
0.2*N_inactive)]
> new_data$exercise[newly_active_patients] <- 0
```

The impact fraction for such an intervention is then calculated using:

```
> impact_fraction(model=model_exercise,data=stroke_reduced,new_data=new_data)
```

```
0.06707932
```

indicating that the health intervention might result in a 6.7% reduction in the rate of strokes. Note that this calculation really refers to the difference in disease risk in two comparable populations, one with a reduced rate of inactivity. Since changing one's behaviour may not completely eliminate cumulative damage due to prior unhealthy lifestyle, this estimated 6.7% might overestimate the impact of the intervention at least in the short term. If the 20% reduction in 'inactivity' is sustained over many years, it is reasonable that this estimate represents a long run effect of the health intervention.

2.4. PAF nomograms

`graphPAF` facilitates plotting of the interrelationships between prevalence, odds ratios and PAFs over multiple risk factors using methods described in detail in Ferguson *et al.* (2019). These plots utilise the concept of 'approximate PAF', derived in the same paper:

$$PAF_{approx} = log(OR)\pi_{control} \approx PAF \tag{8}$$

where OR is the causal odds ratio between a risk factor and disease, and $\pi_{control}$ is the prevalence of the risk factor in controls. This approximation stems from a Taylor expansion of the PAF around a relative risk of 1, and will be most accurate for risk factors that have relatively small effects on a relatively rare outcome. One interesting observation regarding approximate PAFs is the symmetric roles that risk factor prevalence and log odds ratio play in its definition; indicating that similar changes in either lead to a similar impact on disease on a population level. To create a fan plot, risk factor data (names, prevalences and log odds ratios) must be first summarised into an `rf_summary` object before plotting. For instance:

```
> rfs <-  rf_summary(rf_names=c("Hypertension","Inactivity",
"ApoB/ApoA","Diet","waist_hip_ratio","Smoking",
"Cardiac causes","Alcohol","Global Stress","Diabetes"),
rf_prev=c(.474,.837,.669,.67,.67,.224,.049,
        .277,.144,.129),risk=c(1.093,0.501,0.428,0.378,0.294,
         0.513,1.156,0.186,0.301,0.148),log=TRUE)
```

creates such an object for 10 risk factors from the INTERSTROKE database. In the above code, `rf_prev` is a vector of the prevalences of the differing risk factors (named in `rf_names`). While technically, one should use the prevalence of the risk factor in healthy controls without disease in `rf_prev`, this can be substituted with population prevalence if the disease is rare. For risk factors with more than 2 levels (here `ApoB/ApoA`, `waist_hip_ratio` and `alcohol` have 3 levels), the prevalence of the non reference levels of the risk factor should be used. By default, the argument `risk` should specify confounder adjusted log odds ratios or risk ratios for association between risk factor and outcome, although odds ratios or risk ratios can be used via the setting `log=FALSE`. Note that log odds ratios can be conveniently estimated via coefficients from fitted logistic regression models. Plotting this `rf_summary` object, using default settings, produces Figure 1 below.

```
> plot(rfs)
```

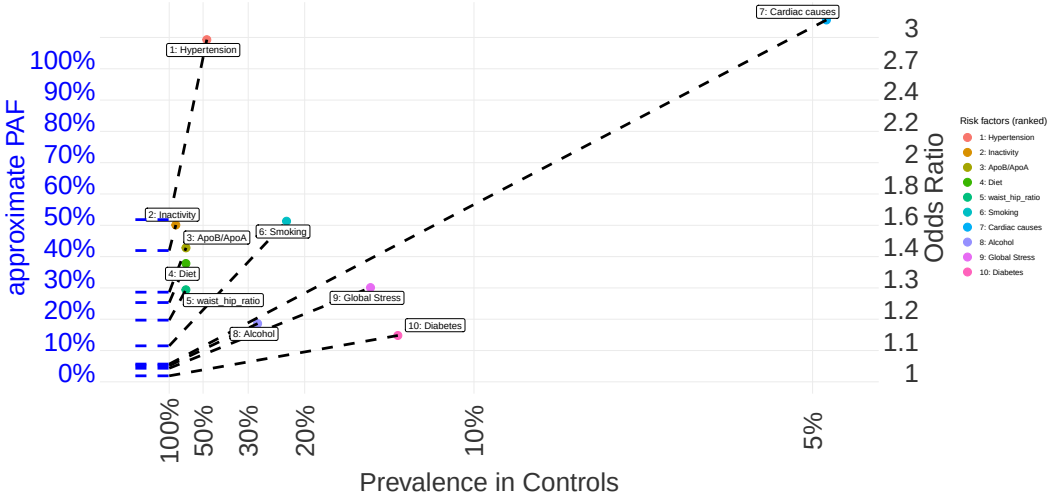


Figure 1: Fan Plot displaying Prevalences, odds ratios and approximate PAFs for INTERSTROKE risk factors. The approximate PAF is represented as both the slope of the line adjoining a point to the y axis, and also the y axis intercept of that adjoining line. The fan plot indicates that hypertension and inactivity are the two most prominent risk factors in stroke pathogenesis. Cardiac disease is an outlier on the plot. While it has the highest estimated relative risk, it has low prevalence (less than 5%) in comparison with the other risk factors and is only ranked 7th in terms of disease burden

The approximate PAF is represented on a fan plot as both the slope of the line adjoining a point to the y axis, and also the y axis intercept of that adjoining line. Fan plots are read clockwise from the upper left corner along the rays of decreasing approximate PAF (which is again the slope of the ray), and display risk factor prevalence and odds ratio (based on the x axis and y axis intercept of a particular point) for the risk factors under comparison, in addition to approximate PAFs.

Imagine now a successful health intervention that reduces the prevalence of smoking by about 50%. This information might be displayed in a `rf_summary` object as follows:

```
> rfs <- rf_summary(rf_names=c("Hypertension","Smoking",
          "Smoking (after health intervention)"),
          rf_prev=c(.474,.224,.11)
          ,risk=c(1.093,0.513,0.513),log=TRUE)
```

Like a fan plot, PAF nomograms display joint information on prevalence, odds ratio and approximate PAF, but this time on three vertical axes, with a risk factor represented by the line connecting these three data points. An intervention will usually work by changing the population prevalence of the risk factor, without affecting the odds ratio. This can be graphically represented by rotating the line for the risk factor through the new prevalence using the (unaffected) odds ratio on the left hand axis as a pivot, as represented by the green and blue lines on Figure 2. The difference in approximate PAFs on the right hand axis in the green and blue line represents the approximate impact fraction for the intervention. Plotting

a `rf_summary` object with argument `type="rn"` produces the Figure below. If preferred, using `type = "n"`, uses odds ratio rather than prevalence as the centre axis, with risk factor prevalence being the left hand axis, but is otherwise interpreted similarly.

```
> plot(rfs,type="rn")
```

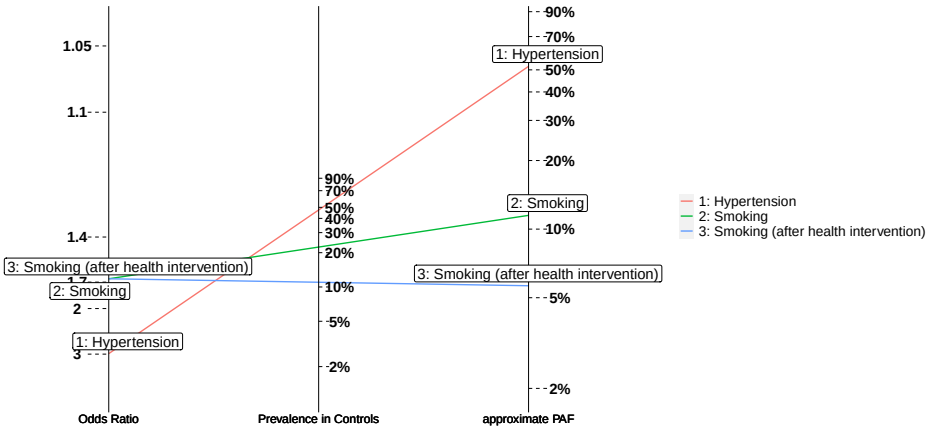


Figure 2: PAF nomogram for INTERSTROKE risk factors. Nomograms like the above give an alternative way to display joint intervention regarding odds ratios, prevalences and approximate PAFs. They can also be used to visualise interventions. For instance, the green and blue lines represent smoking in a population pre and post intervention. The odds ratio for smoking isn't affected by the intervention, but the prevalence for smoking is. The effect of the intervention for smoking PAF can be visualised by rotating the line for smoking (using the left axis odds ratio as a pivot) through the new prevalence post intervention.

3. Estimation with Continuous Exposures

Frequently, a discrete risk factor such as hypertension is generated by truncating an underlying continuous exposure, such as blood pressure. Not accounting for this underlying continuity may result in underestimation of disease burden attributable to the exposure as some individuals with the reference value of the discretised risk factor may still be at elevated risk. For instance if hypertension is defined as systolic blood pressure above 140mm/Hg, an individual with systolic blood pressure of 139mm/Hg would fall into the reference group but might have increased risk of cardiovascular disease compared to an individual with systolic blood pressure under 120mm/Hg. Ferguson *et al.* (2020a) discusses these issues and suggests a variety of appropriate estimands for the level of disease burden due to continuous exposures.

Using the notation from Ferguson *et al.* (2020a), we consider the exposure for a randomly selected individual from the population as a continuous random variable, X, with Y representing a binary disease outcome. We let Y_x represent the potential outcome if $X = x$, which

we assume is well defined. Assuming that $P(Y_x = 1)$, considered as a function of x, has some minimum value x_{min} within the physiological limits of the exposure X, we define the PAF as:

$$PAF = \frac{P(Y = 1) - P(Y_{x_{min}} = 1)}{P(Y = 1)}. \tag{9}$$

In the circumstance that $P(Y_x = 1)$ is strictly decreasing or strictly increasing as a function of x, the minimum value x_{min} may be undefined, in which case we define the PAF as:

$$PAF = \frac{P(Y = 1) - \text{Inf}\{P(Y_x = 1)\}}{P(Y = 1)}, \tag{10}$$

defining $\text{Inf}\{P(Y_x = 1)\}$ as the infimum of the set of probabilities $P(Y_x = 1)$ with x ranging over the possible range of exposure values.

As explained in Ferguson *et al.* (2020a), the estimands (9) and (10) may be difficult to estimate when x_{min} falls in the extremes of the exposure distribution. As an alternative, the family of estimands: PAF_q for $q \in (0, 1)$ are suggested as alternative metrics. Intuitively PAF_q is the impact fraction for an intervention that shifts the exposure value for individuals in the subpopulation where it is beneficial to do so, with the intervention not effecting individuals where such a shift is not necessary. $1-q$ indicates the proportion of individuals affected by the intervention, in addition to how large the shift in exposure values is for those affected (larger values of $1 - q$ indicating larger shifts). More technically, exposure values X for individuals whose disease risk (based purely on the exposure value and not on other covariates) is above the $100q^{th}$ percentile of disease risk are moved to the closest possible value, $f_q(X)$, where closest implies $\mid f_q(X) - X \mid$ as small as possible, such that the disease risk associated with exposure values of $f_q(X)$ is at or below the $100q^{th}$ percentile. Individuals with good exposure values (corresponding to risk values below the $100q^{th}$ percentile), are unaffected by this intervention. PAF_q when $q > 0$ tends to be easier to estimate than PAF (9), the reason being that estimating PAF_q usually involves less extrapolation. It also has a more concrete real world interpretation as the impact fraction for an achievable intervention. PAF_q is defined more precisely as:

$$PAF_q = \frac{P(Y = 1) - P(I\{X \in R_q\}Y + I\{X \notin R_q\}Y^{f_q(X)} = 1\}}{P(Y = 1)} \tag{11}$$

where R_q is the interval of exposure values corresponding to the bottom $100q\%$ of risk and $f_q(X)$ is the closest point in the closure of R_q to X. Note that as $q \downarrow 0$, $PAF_q \uparrow PAF$.

Under continuous analogs of the conditions 1., 2. and 3. listed on pages 3 and 4, (11) can be estimated as

$$PAF_q = \frac{E_C(I\{X \notin R_q\}(\hat{P}(Y = 1 \mid X, C) - \hat{P}(Y = 1 \mid \hat{f}_q(X), C)))}{P(Y = 1)} \tag{12}$$

and

$$PAF_q = E_{X,C|Y=1} I\{X \notin R_q\}[1 - \frac{\hat{P}(Y = 1 \mid \hat{f}_q(X), C)}{\hat{P}(Y = 1 \mid X, C)}] \tag{13}$$

and

$$\hat{PAF}_q(t) = \frac{\sum_{i \leq N} (e^{-\hat{H}_0(t)\hat{h}(C_i, A_i)} - e^{-\hat{H}_0(t)\hat{h}(C_i, \hat{f}_q(X))})}{\sum_{i \leq N} e^{-\hat{H}_0(t)\hat{h}(C_i, X_i)}} \tag{14}$$

respectively for cross sectional, case-control and cohort designs, with $\hat{f}_q(x)$ the estimated value for $f_q(x)$ and $\hat{P}(Y = 1 \mid x, c)$, the estimated probability of disease, when the risk factor is x and the covariates are c.

`graphPAF` uses these equations to estimate PAF_q across differing risk factors. Here we consider the convenient case where a group of continuous risk factors: `waist_hip_ratio`, `diet` and `lipids` all have the same set of underlying confounders, and subsequently estimated effects of each risk factor can be obtained from a single statistical model. The following code demonstrates how such a model might be specified for a case-control dataset:

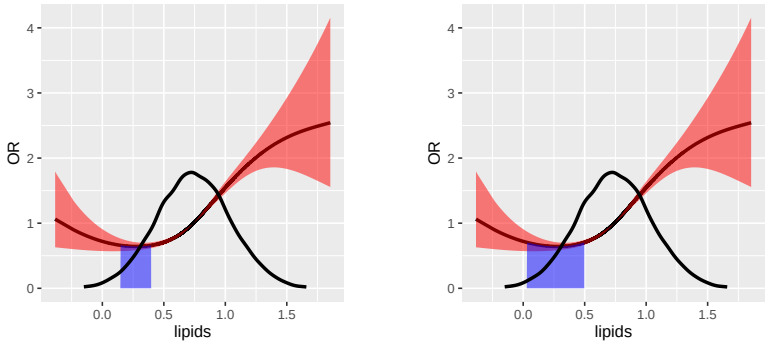
```
> model_continuous_clogit <- clogit(formula = case ~
region*ns(age, df = 5) + sex*ns(age, df = 5) + education +
exercise + ns(diet, df = 3)  + alcohol +
stress + ns(lipids,df = 3) + ns(waist_hip_ratio, df = 3) +
 high_blood_pressure + strata(strata), data = stroke_reduced)
```

In the above, the continuous exposures `waist_hip_ratio`, `diet` and `lipids` appear in the model as natural spline terms in the model. One can evaluate the estimated shape of the exposure/outcome relationship, and visualise the interventions corresponding to a particular value of PAF_q using the function `plot_continuous`. As an example:

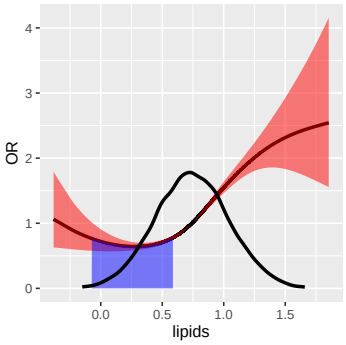
```
> plot_continuous(model_continuous_clogit,riskfactor="lipids",
    data=stroke_reduced,min_risk_q=.1)
> plot_continuous(model_continuous_clogit,riskfactor="lipids",
      data=stroke_reduced,min_risk_q=.2)
> plot_continuous(model_continuous_clogit,riskfactor="lipids",
   data=stroke_reduced,min_risk_q=.3)
```

produces estimated relationships between lipids and OR of stroke (with the median value for lipids as a reference by default), highlighting the regions representing the post intervention ranges of the risk factor for $PAF_{0.1}$,$PAF_{0.2}$ and $PAF_{0.3}$ (the argument `min_risk_q` identifying the post intervention range).

Having fit the model, the function `PAF_calc_continuous` can be used to estimate PAF_q. Mandatory arguments to this function are `riskfactor_vec`, a vector of the risk factor names that are of interest, `q_vec`, a vector of q values at which calculate PAF_q as well as the model and dataset. The resulting object is essentially a data frame with rows for each risk factor, PAF_q combination and columns corresponding to quantiles which can be printed and plotted as follows:



(a) $PAF_{0.1}$ (b) $PAF_{0.2}$



(c) $PAF_{0.3}$

Figure 3: Estimated effects of blood lipid levels on the OR of stroke. The density of lipids and pointwise 95% confidence bands for the odds ratios are also plotted. Also shaded blue are the target regions for the intervention associated with PAF_q for various q. For instance $PAF_{0.1}$ corresponds to the smallest 10% of risk

```
> out <- PAF_calc_continuous(model=model_continuous_clogit,
data=stroke_reduced, riskfactor_vec=c("diet","lipids","waist_hip_ratio"),
q_vec=c(0.01, 0.1,0.3,0.5,0.7,0.9),ci=TRUE)
> print(out)
```

	riskfactor	q_val	est	bias	debiased_est	norm_lower	norm_upper
1	diet	0.01	0.16200	2.85e-02	0.13300	0.042300	0.2240
2	diet	0.10	0.14600	3.91e-03	0.14200	0.096300	0.1880
3	diet	0.30	0.11100	4.16e-04	0.11100	0.075800	0.1460
4	diet	0.50	0.07990	-2.17e-04	0.08010	0.063000	0.0973
5	diet	0.70	0.04860	-8.75e-04	0.04950	0.034800	0.0642
6	diet	0.90	0.01600	-5.33e-04	0.01660	0.007890	0.0252
7	lipids	0.01	0.37900	8.24e-03	0.37100	0.333000	0.4090
8	lipids	0.10	0.36500	6.27e-03	0.35800	0.326000	0.3910
9	lipids	0.30	0.28200	5.31e-03	0.27700	0.251000	0.3030
10	lipids	0.50	0.17300	3.56e-03	0.17000	0.151000	0.1890
11	lipids	0.70	0.07330	4.88e-04	0.07280	0.056900	0.0887

```
12          lipids  0.90 0.01290 -5.19e-04      0.01350   0.005190     0.0217
13 waist_hip_ratio  0.01 0.17200  1.75e-02      0.15500   0.062600     0.2460
14 waist_hip_ratio  0.10 0.16100  1.74e-03      0.15900   0.112000     0.2050
15 waist_hip_ratio  0.30 0.11400  5.81e-04      0.11400   0.083100     0.1450
16 waist_hip_ratio  0.50 0.06810  1.09e-03      0.06700   0.048600     0.0855
17 waist_hip_ratio  0.70 0.03080  2.96e-04      0.03050   0.016400     0.0445
18 waist_hip_ratio  0.90 0.00691  2.98e-05      0.00688  -0.000203     0.0140
```

As explained earlier, the default setting `"calculation_method="B"` (13) facilitates estimation in case-control designs for rare diseases. In contrast, `"calculation_method="D"` which uses (12) is appropriate in cross-sectional designs or for case-control settings where disease prevalence is known, and (14) is appropriate for cohort studies with a survival response. Note that in the case of a survival response, $PAF_q(t)$ can only be evaluated at a single time, t, specified as `t_vector` being a single element. Plotting estimated PAF_q, which can be done by simply applying `plot` to a `PAF_q` object, against q for several risk factors allows the user to assess the relative benefits of comparable and achievable interventions on differing risk factors.

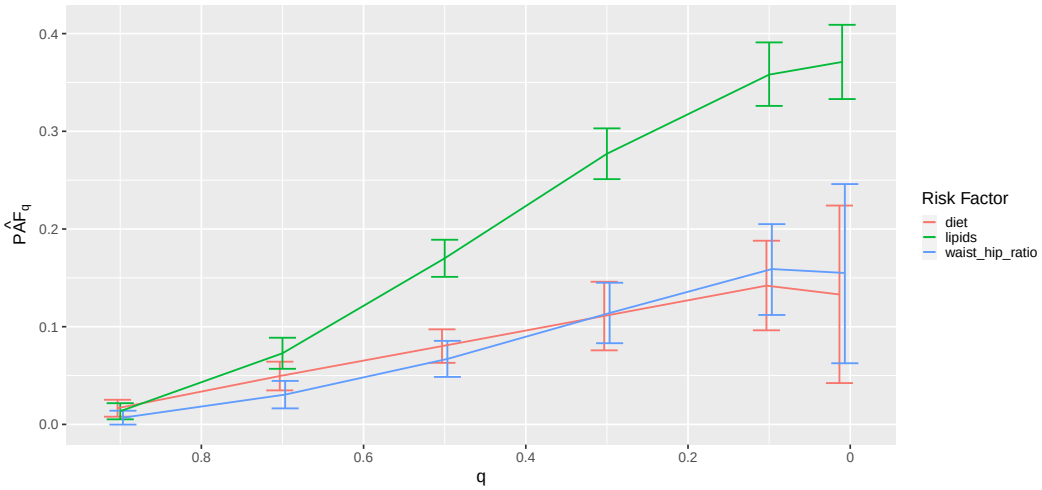


Figure 4: plotting PAF_q over multiple risk factors. The figure indicates that comparable interventions on diet and waist hip ratio (for instance shifting 50% of exposure values as is the case in $PAF_{0.5}$ may have similar effects for diet and waist hip ratio, but much larger effects for lipids). As can be seen in the plot, the confidence intervals get wider as q gets smaller reflecting the fact that PAF_q (for $q \geq 0.1$) is easier to estimate than $PAF_0 = PAF$ in addition to representing more realistic interventions.

The results from the plot (shown in Figure 4) indicate that comparable interventions targeting waist hip ratio and diet may have similar effects on disease burden, with interventions on lipids having larger effects. This might motivate an intervention on lipid levels (for example, increased statin use when appropriate) over interventions on diet or BMI, although admittedly many other factors may dictate what if any intervention may be chosen in practice.

4. Pathway-specific PAF calculations

While the PAF provides an overall measure of the importance of a particular disease risk factor in causing disease on a population level, the mechanisms by which the risk factor effects disease may also be of interest. For instance, perhaps physical inactivity increases blood pressure which subsequently increases the risk of stroke. Alternatively, physical inactivity might indirectly increase the risk of stroke through weight gain or increased cholesterol levels. In this context, the variables blood pressure, weight gain and cholesterol are regarded as 'mediators', that is they are intermediate variables on differing causal pathways each partially explaining the causal relationship between inactivity and stroke. How important might each pathway be in disease pathogenesis? In O'Connell and Ferguson (2022) this question is addressed by defining a PAF for a particular mediating pathway. Roughly this 'pathway-specific' PAF (PS-PAF for short) can be interpreted as the relative decrease in disease prevalence if a particular mediating pathway didn't exist. For instance imagine there was no effect of physical inactivity on blood pressure; what percentage of stroke might be avoided in such a population? Letting $M^1, ..., M^K$ represent K known mediators of the risk factor outcome relationship, $A \in \{0, 1\}$ a risk factor and $Y \in \{0, 1\}$ a disease outcome, the PS-PAF for mediator $k \leq K$ is denoted as:

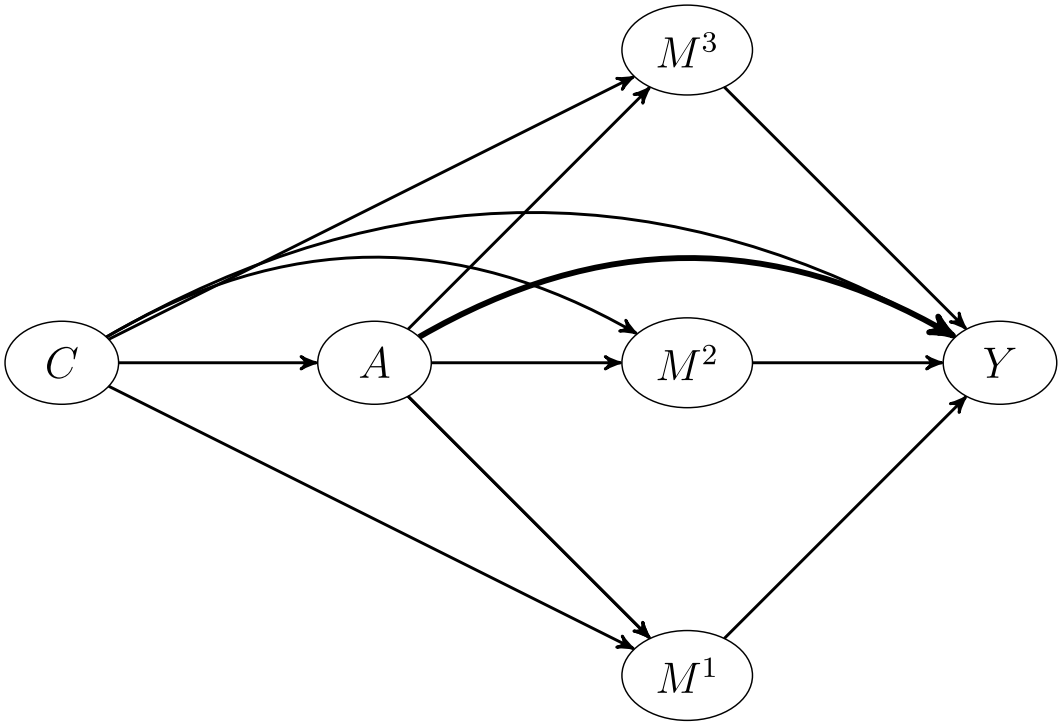


Figure 5: Mediators on separate causal pathways. M^1, M^2 and M^3 mediate the causal relationship between A and Y. These mediators represent independent mechanisms by which A affects Y in that any pathway of direct arrows originating from A and ending at Y can only involve one of the three mediators.

$$PAF_{A->M^k->Y} = \frac{P(Y=1) - P(Y_{A,M_0^k}=1)}{P(Y=1)} \tag{15}$$

$P(Y_{A,M_0^k} = 1)$ can be interpreted as disease prevalence in a hypothetical population which

mirrors the actual population in the values of the risk factor A, but where the values for mediator, M^k, behave as if the risk factor didn't exist (note that on an individual level M_0^k is the potential outcome for the k^{th} mediator assuming no exposure to the risk factor, that is $A = 0$). As described in O'Connell and Ferguson (2022), interpretations for pathway-specific PAFs subtly differ based on the causal identifiability conditions assumed. We are describing the mechanistic interpretation here, although two other interpretations exist. We won't go into these details here and instead refer the interested reader to O'Connell and Ferguson (2022).

In addition to defining pathway-specific PAFs for indirect pathways, one can also define an PAF for all 'unobserved' or unknown pathways:

$$PAF_{A->Y} = \frac{P(Y=1) - P(Y_{0,M^1,...,M^K} = 1)}{P(Y=1)} \tag{16}$$

(16) denotes the 'direct' pathway specific PAF, and represents the contribution of mechanisms by which the risk factor affects disease, other than those represented by pathways through M^1,....,M^K (Note that $P(Y_{0,M^1,...,M^K} = 1)$ can be interpreted as the disease prevalence in a population where the risk factor, A, was eliminated but with the joint distribution of mediators $M^1, ..., M^K$ being unaffected).

Under the assumptions listed in O'Connell and Ferguson (2022) (with the additional assumption that mediators are on separate causal pathways between the risk ractor and disease), estimating (15) requires fitting a model for the mediator, M^k, conditional on both the risk factor, A, and the confounder vector for the exposure outcome relationship, C. Note that these models estimate $P(M^k = m \mid A, C)$ for a discrete mediator and $E(M^k \mid A, C)$ for a continuous mediator. In addition, one needs to fit a model for the disease outcome, Y, conditional on the exposure, A, mediators, $M^1, ..., M^K$, and the same set of confounders, C. This second model estimates $P(Y = 1 \mid A, C, M^1, ..., M^K)$. When M^k is continuous, the following estimator for (15) can then be used:

$$\widehat{PAF}_{A->M^k->Y} = \frac{\sum w_i Y_i - \sum_i w_i P(Y = 1 \mid \widehat{A_i, C_i}, \hat{M}_i^k, \mathbf{M_i^{\neq k}})}{\sum w_i Y_i} \tag{17}$$

with $\hat{M}_i^k = M_i^k - E(M^k \mid \widehat{A = 0, C_i})$, with C_i and M_i^k representing the observed values of the confounder vector and k^{th} mediator for person i, and $\mathbf{M_i^{\neq k}}$, the observed values for other mediators for the same individual. Weights w_i are used to account for possible case-control structure. For representative cross sectional samples, these weights should be set to 1 (the default). In contrast, for case-control data, these weights can be set based on estimated disease prevalence. In the case that the mediator is discrete, a slightly different estimator is used:

$$\widehat{PAF}_{A->M^k->Y} = \frac{\sum w_i Y_i - \sum_i w_i \sum_{m \in \mathcal{M}^k} P(M^k = \widehat{m \mid A_i} = 0, C_i) P(Y = 1 \mid A_i, \widehat{C_i, M^k} = m, \mathbf{M_i^{\neq k}})}{\sum w_i Y_i} \tag{18}$$

Direct PS-PAF is slightly easier to estimate, as one only needs to fit the outcome model that conditions on the risk factor, A, covariates, C, and mediators, M^1,...,M^K:

$$\widehat{PAF}_{A->Y} = \frac{\sum w_i Y_i - \sum_i w_i P(Y = 1 \mid A_i = \widehat{0, C_i}, M_i^1, ..., M_i^K)}{\sum w_i Y_i} \tag{19}$$

Examples

To illustrate these calculations with `graphPAF`, suppose we wish to estimate pathway-specific PAFs for the 4 pathways from physical inactivity to stroke through waist hip ratio, through blood lipid counts, through high blood pressure, and through any mediating pathways other than waist hip ratio, blood pressure and lipids from the simulated dataset `stroke_reduced` included in the `graphPAF` library. Since `stroke_reduced` is a case-control dataset, weighted models for each mediator and the response need to be fit to replicate what one would expect from a representative sample of the population. In `stroke_reduced`, these weights are already in the dataset and are based on an average incidence of 0.0035 new strokes per person per year (as explained earlier). To calculate the `weights` vector for a different prevalence, `stroke_reduced` could be sent to the `data_clean` function. For instance, if we instead thought that 0.01 was the correct incidence, we could use

```
stroke_reduced_2 <- data_clean(stroke_reduced,
riskfactor_vec=colnames(stroke_reduced),prev=0.01)
```

A column of weights would then be included in the dataframe `stroke_reduced_2`. Having calculated these weights, models for the response and a list of models for the mediators can be specified:

```
> response_model <-
glm(case ~ region * ns(age, df = 5) + sex * ns(age, df = 5) +
         education + exercise + ns(diet, df = 3) + smoking + alcohol +
          stress + ns(lipids, df = 3) + ns(waist_hip_ratio, df = 3) +
          high_blood_pressure,data=stroke_reduced,family='binomial',
           weights=weights)
> mediator_models <- list(
    glm(high_blood_pressure ~ region * ns(age, df = 5) +
    sex * ns(age, df = 5) + education   +exercise + ns(diet, df = 3) +
     smoking + alcohol + stress,data=stroke_reduced,family='binomial',
     weights=weights),
    lm(lipids ~ region * ns(age, df = 5) + sex * ns(age, df = 5) +
    education +exercise + ns(diet, df = 3) + smoking + alcohol +
     stress, weights=weights, data=stroke_reduced),
    lm(waist_hip_ratio ~ region * ns(age, df = 5) +
    sex * ns(age, df = 5) + education+ exercise + ns(diet, df = 3) +
    smoking + alcohol + stress, weights=weights,
       data=stroke_reduced))
```

The response model (argument: `response_model`) and list of mediator models (`mediator_models`)), along with the standard arguments for the riskfactor name, reference value for the risk factor and dataset, are then sent to `ps_paf`, which implements the estimators: (17),(18) or (19) with the fitted models. Again, for case-control datasets, the argument `prev` needs to be specified for correct calculation of the weights.

```
> ps_paf(response_model=response_model, mediator_models=mediator_models,
         riskfactor="exercise",refval=0,data=stroke_reduced,prev=0.0035,ci=TRUE)
```

```
                      est      bias debiased_est norm_lower norm_upper
Direct             0.3350  0.005050       0.3300   0.260000     0.3990
high_blood_pressure 0.0174 -0.001200       0.0185  -0.00605     0.431
lipids             0.0207  0.000713       0.0200  -0.000896     0.0409
waist_hip_ratio    0.0314  0.000390       0.0310   0.019100     0.0429
```

The results indicate that only a small proportion of the disease burden due to physical inactivity is attributable to pathways involving lipids, blood pressure and waist hip ratio. For instance, if the pathway from physical inactivity to stroke through waist hip ratio were disabled (in that physical inactivity had no deleterious affect on waist hip ratio), relative stroke prevalence would only decrease by 3.1%, with similar interpretations and small PS-PAFs for the pathways through lipids and high blood pressure.

5. Joint PAF

Joint PAFs refer to the collective disease burden that can be appropriated to a collection of risk factors. For instance the INTERSTROKE study O'Donnell *et al.* (2016) estimates that roughly 90% of incident strokes might be avoided if 10 major modifiable stroke risk factors were removed from the population. More formally, the joint PAF for a set of risk factors, $\mathbf{S}$ can be defined as:

$$PAF_{\mathbf{S}} = \frac{P(Y=1) - P(Y(\mathbf{0_S})=1)}{P(Y=1)}, \tag{20}$$

with the shorthand: $Y(\mathbf{0_S})$ representing the potential outcome where the subset of risk factors $\mathbf{S}$ have been set to their reference levels. Traditionally, such calculations were performed via multivariable regression models that include the set of variables that are to be eliminated. For instance to estimate a joint PAF for stroke associated with stress and a diagnosis of diabetes, disease risk in the data collected might be compared to predicted disease risk if diabetes status and stress were set to their reference levels, with the predicted disease risk being computed via a single fitted logistic model. While this approach may be fine if diabetes status and stress share the same set of confounding variables (proviso that the model for stroke risk includes these confounders and is correctly specified), bias may result when the effects of one of the risk factors act as confounders in the relationship between the response and other risk factors of interest. This is the case here as blood pressure, which is an effect of physical activity according to Figure 6, confounds the relationship between diabetes and stroke. For these kinds of causal structures, while predicted risks derived via a single regression may correctly reflect the probability that an individual in the dataset has disease, *conditional* on their having reference values for the risk factors under investigation, they will not reflect the probability of disease in the population if all individuals had reference levels for those same risk factors. In other words, the associated estimated joint PAF will not have a causal interpretation.

Ferguson *et al.* (2020b) describes how the intervention corresponding to a joint PAF (the intervention being the 'elimination' of a subset of risk factors) can be conceptualised via recursive application of Pearl's do-operator Pearl (2009) on the true causal graph (assumed to be a directed acyclic graph or DAG), linking risk factors, outcome and associated risk

factor/outcome confounders. This observation facilitates asymptotically unbiased estimation of joint PAFs under general causal structures. To achieve this in practice, we need to first know the causal DAG, second have collected data on individuals $i = 1, ..., N$ for all variables represented in the DAG, and finally correctly specify and fit statistical models linking each node in the causal DAG to all of its direct causes (the direct causes being those variables with arrows pointing to the node of interest). Having done this, one can use these fitted models to simulate from the joint distribution of all variables in the graph (confounders, risk factors and outcome) corresponding to each application of the do-operator. For each application of the do-operator (corresponding to a population level elimination of a single risk factor), this simulation is itself recursive. For instance, if smoking is eliminated, smoking is first set to its reference level (no smoking) for all individuals in the current simulated dataset. Values for the direct effects of smoking (that is the nodes for which smoking is a parent in the causal graph) are then simulated from the conditional distribution of these variables assuming no smoking. Supposing blood pressure is one of the effects of smoking, next the direct effects of blood pressure are simulated, conditional on the simulated values for blood pressure and the other direct effects of smoking. This process (simulations of a particular node being made conditional on the simulated values for parent nodes) is continued until the response node is simulated. More details are given in Ferguson *et al.* (2020b).

Suppose then that upon elimination of a subset $\mathbf{S}$ of risk factors, the population distribution of all variables in the causal graph is $\mathbf{P_S}$, and via the recursive algorithm above, we have simulated new data $\mathbf{D_S}$ for all variables in the causal graph (excluding the response) under $\mathbf{P_S}$. Our estimate for (20) is then:

$$PAF_{\mathbf{S}} = \frac{\sum_{i \leq N}[w_i Y_i - w_i \hat{P}(Y_i = 1 \mid \mathbf{D_S})]}{\sum_{i \leq N} w_i Y_i}, \tag{21}$$

where $\hat{P}(Y_i = 1 \mid \mathbf{D_S})$ represents the estimated probability of disease for individual i under the simulated data structure for risk factors and confounders represented by $\mathbf{D_S}$ (this probability depends on $\mathbf{D_S}$ through the simulated values for individual i at those risk factors and covariates that are assumed to directly affect the outcome). This approach can be applied to cross sectional and case-control datasets, where as before the argument `prev` is utilised to calculate the weights, w_i in case-control datasets. Note that the above estimator may be randomised, that is estimating joint PAF twice using the same data may give slightly different results, since differing simulated datasets $\mathbf{D_S}$ will likely be used in (20) on each ocassion. The degree of randomisation in the resulting estimator will generally be small for large datasets, although if desired the estimator (21) can be averaged over several independently simulated versions of $\mathbf{D_S}$ to reduce variability. In some cases, $\mathbf{D_S}$ may not vary over over differing simulations. For instance, for reasons described in O'Connell and Ferguson (2022), continuous variables in $\mathbf{D_S}$ are simulated by adding model predicted residuals to the predicted values given the current values of their parents. As a result, randomness in $\mathbf{D_S}$ can only be generated by discrete risk factors or confounders that are graph descendants of risk factors that are eliminated.

5.1. Data examples

The `joint_paf` function in graph PAF implements the procedure described above. As an example, suppose we are interested in estimating the joint PAF for stroke due to stress and blood pressure. First we need to specify the causal graph linking stress, blood pressure

and stroke. In doing this, one must ensure that the confounders of any two nodes in the graph are also specified: for instance, any joint causes of stress and blood pressure must also be included. In Figure 5, we illustrate our assumed causal structure for INTERSTROKE risk factors, which includes many confounders and risk factors other than stress and blood pressure. However, in the context of this estimation problem (and assuming Figure 5 is correct), we can give `graphPAF` a reduced causal structure: we actually don't need to specify preclinical disease variables `PCD` or physiology variables `P`, other than blood pressure, since they are not common causes of variables in the set {stress, blood pressure and stroke}. We can specify the causal graph with a list of the parents of all relevant variables in the graph using the argument `parent_list`, together with a vector of variable names corresponding to the nodes of the graph using the argument `node_vec`. When doing this it is important that the components of `node_vec` and `parent_list` are in the same order. In addition, `node_vec` should be ordered so that parent nodes, which represent the causes of their children nodes, are positioned in the vector before their children.

```
> node_vec=c("exercise","diet","smoking","alcohol","stress",
      "high_blood_pressure","case")
> parents_exercise <- c("education")
> parents_diet <- c("education")
> parents_smoking <- c("education")
> parents_alcohol <- c("education")
> parents_stress <- c("education")
> parents_high_blood_pressure <- c("education","exercise","diet",
       "smoking","alcohol","stress")
> parents_case <- c("education","exercise","diet","smoking",
       "alcohol","stress","high_blood_pressure")
> parent_list <- list(parents_exercise,parents_diet,parents_smoking,
  parents_alcohol,parents_stress,parents_high_blood_pressure,parents_case)
```

Next, models for each variable, each model adjusting for the parents of that variable as well as the variable itself, need to be fit. In estimating joint PAFs (as well as the sequential and average PAFs detailed in the following section), `graphPAF` supports simulation from linear models (fit using `lm`), logistic models (fit using `glm`) and ordinal logistic models (fit using `polr` from the *R* library `MASS`). Given that specification of multiple models can be time consuming, `graphPAF` has a function `automatic_fit` that automatically fits additive models for each node in `node_vec`, conditioned on the parents of that node. This function can also fit nonlinear relationships for continuous risk factors or confounders using the `spline_nodes` argument. In the code below, `diet` is assumed to have a nonlinear effect. Common interactions between variables that appear in all of the models can be specified by the argument `common`. In the case that the models for differing nodes require individual specification (for example if the interaction terms differ between models), the models can be fit separately with either `lm`, `glm` or `polr`, before populating `model_list`. For case-control datasets, these models need to be fit with appropriate weighting (so that the weighted dataset set could be regarded as a representative sample) as described earlier. If `automatic_fit` is used, this can again be achieved automatically by specifying the `prev` argument. As mentioned earlier, weights can be also calculated by passing the original dataset to `data_clean` before model fitting.

```
> model_list=automatic_fit(data=stroke_reduced, parent_list=parent_list,
      node_vec=node_vec, prev=.0035,common="region*ns(age,df=5)
      +sex*ns(age,df=5)",spline_nodes=c("diet"))
```

Having specified values for `model_list`, `parent_list` and `node_vec`, these values can be passed as arguments to `joint_paf` to estimate the joint PAF. The subset of risk factors of interest, `riskfactor_vec` which will be a subset of `node_vec`, also needs specification. For case-control data sets we also need to specify the argument `prev`. All of these arguments are common to `joint_paf`, and the related functions `seq_paf` and `average_paf` described later in Section 6. As an example, below we compare estimated single risk factor PAFs for smoking and blood pressure to the joint PAF for both smoking and blood pressure together. Note that the estimated joint PAF (0.375) is slightly less than the sum of individual PAFs (0.113+0.269=0.382). This is expected Rowe, Powell, and Flanders (2004) as some of the disease cases that might be prevented in a population where nobody smokes would equally be prevented in a population where nobody was hypertensive. As mentioned earlier, `joint_paf` can average (21) over multiple independently estimated datasets using the argument `nsim`. However, since no discrete graph descendants of `smoking` (other than `high_blood_pressure`) are specified in the causal graph specified in `joint_paf`, $\mathbf{D_S}$ will not vary over differing simulation iterates in this example.

```
> joint_paf(data=stroke_reduced, model_list=model_list,
parent_list=parent_list,node_vec=node_vec,riskfactor_vec=c("smoking"),
 prev=.0035,ci=TRUE)
```

```
            est    bias debiased_est norm_lower norm_upper
joint PAF 0.113 0.00718        0.105     0.0857      0.125
```

```
> joint_paf(data=stroke_reduced, model_list=model_list,
parent_list=parent_list, node_vec=node_vec,
riskfactor_vec=c("high_blood_pressure"),
 prev=.0035,ci=TRUE)
```

```
            est    bias debiased_est norm_lower norm_upper
joint PAF 0.269 0.00331        0.266      0.248      0.284
```

```
> joint_paf(data=stroke_reduced, model_list=model_list,
parent_list=parent_list, node_vec=node_vec,riskfactor_vec
=c("smoking","high_blood_pressure"), prev=.0035,
            ci=TRUE)
```

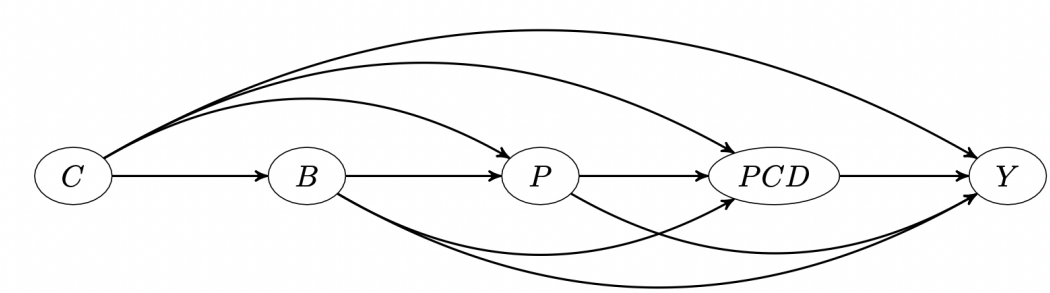


Figure 6: DAG showing causal structure linking risk factors at multiple levels. For the simulated INTERSTROKE dataset, we might assume that each node represents multiple risk factors as follows: C represents the Confounders (age,region,sex and education), B represents Behavioural risk factors: (exercise, alcohol use, smoking, stress levels and diet), P represents risk factors indicating physiology: (blood pressure, blood lipids and waist hip ratio), PCD represents preclinical disease: (diabetes and cardiac symptoms such as atrial fibrillation). Y is a 0/1 indicator for stroke occurrence

```
               est     bias debiased_est norm_lower norm_upper
joint PAF 0.375 0.000738        0.374      0.349      0.399
```

6. Sequential and Average PAFs

Sequential PAFs (SAF)s, first described by Eide and Gefeller (1995) are closely related to joint PAFs as discussed in the previous section. They pertain to the incremental disease burden attributable to a risk factor (or more specifically to the removal of that risk factor from the population) in a population where a subset of risk factors have already been eliminated. Suppose that we number disease risk factors under consideration as: $\{1, ..., K\}$. We can define the sequential PAF for eliminating risk factor $j \leq K$, conditional on the subset of risk factors $\mathbf{S} \subset \{1, ..., K\} \setminus \{j\}$ already having being removed from the population, as the difference in joint PAF pertaining to removing $\mathbf{S} \cup \{\mathbf{j}\}$ and the joint PAF pertaining to removing $\mathbf{S}$ alone:

$$PAF_{j|\mathbf{S}} = PAF_{\mathbf{S}\cup\{j\}} - PAF_{\mathbf{S}} \tag{22}$$

Given this link between joint PAF and sequential PAF, the same issues (in particular risk factors of interest acting as confounders of causally downstream risk factors of interest) mentioned in the section above can also cause biases in estimating sequential PAF and average PAF. These can again be handled by recursive application of the do-operator and simulation from the corresponding distributions. Sequential PAF may be of practical interest if population health interventions are to be applied incrementally (for instance, what would be the next risk factor to target in a health intervention after a successful intervention that targets smoking?), but another use is in the definition and estimation of average PAFs (APAF)s, again first introduced in Eide and Gefeller (1995).

As explained above, individual PAFs for differing risk factors in a set are not expected to sum to the joint PAF corresponding to eliminating all of the risk factors. Over the years, differing proposals have been made to construct versions of PAFs for individual risk factors that do sum to the corresponding joint PAF, the most convincing of which is to define and calculate average PAFs. Again suppose there are K risk factors, labeled again $\{1...K\}$. Imagine eliminating these K risk factors in some sequence. This can be done in $K!$ different ways. Each of these $K!$ permutations can be represented as $\sigma = \sigma(1), ..., \sigma(K)$, where $\sigma(j) = k$ if the risk factor k is the j^{th} risk factor eliminated according to that ordering, and as such each permutation is associated with a sequential PAF for each risk factor. For instance, in the previous example the sequential PAF for risk factor k according to σ would be $SAF_{k|\{\sigma(1)...\sigma(j-1)\}}$ if $j \geq 2$ or just the PAF for risk factor k if $j = 1$. The average PAF, $APAF_k$, for risk factor k is the average of the sequential PAFs over all $K!$ different permutations. By definition, the sequential PAFs for differing risk factors corresponding to a particular permutation must add to the joint PAF. From this it follows easily that the average of these sequential PAFs for each risk factor across differing permutations (that is the average PAF) must also sum over differing risk factors to the joint PAF.

6.1. Estimation

At first look, it seems that one must calculate $K!$ differing sequential PAFs to calculate average PAF for a risk factor. However, examining (22) we see that any sequential PAF is the difference between two differing joint PAFs. The number of joint PAF calculations is the same as the number of nonempty subsets of $\{1...K\}$ (that is $2^K - 1$, much smaller than $K!$). Provided the number of risk factors isn't too large (say 10 or fewer), it is quite feasible to calculate all possible sequential PAFs utilising this approach. The average PAF for risk factor $k \leq K$ can then be calculated using:

$$APAF_k = \frac{\sum_{j=1}^{K}(K-j)!(j-1)!\sum_{\mathbf{S}\subset\{1,...,K\}\setminus k:|\mathbf{S}|=j-1} PAF_{k|\mathbf{S}}}{K!}. \tag{23}$$

The 'exact' approach to estimating $APAF_k$ is to first estimate $PAF_{k|\mathbf{S}}$ for all possible subsets: $\mathbf{S} \subset \{1, ...K\} \setminus k$ of risk factors sets that exclude k, and then plug these estimates into (23). This is done most efficiently when calculating $APAF$ for all K risk factors together.

When 2^K is very large, estimating (23) exactly may be too time consuming. Recognizing instead that $APAF_k$ is a 'population' average of $K!$ sequential PAFs, each sequential PAF corresponding to a single permutation (with admittedly many of these permutations lead to the same SAF), one can approximate the average PAF by randomly sampling a smaller number `nperm` $K!$ of permutations. Obviously, the larger `nperm` is, the smaller the approximation error from this step, which like any sample average decreases probabilistically at rate $\frac{1}{\sqrt{nperm}}$ as `nperm` increases. In practice, `nperm`= 1000 has been suggested to achieve acceptable accuracy Ferguson *et al.* (2018). Stratified sampling of permutations (ensuring for instance that each risk factor appears in position 1 in the elimination order an equal number of times in the `nperm` permutations) can somewhat reduce the approximation error. We will describe this in the next section.

6.2. Examples

Let's extend the example from earlier where we looked at the joint PAF for `smoking` and

high_blood_pressure, to include a 3rd risk factor diabetes. Note that lipids and waist_hip_ratio are joint causes of diabetes and stroke (see Figure 5), and we now need to extend our causal graph and associated list of statistical models to include these variables in addition to diabetes.

```
> node_vec=c("exercise","diet","smoking","alcohol","stress",
      "high_blood_pressure","waist_hip_ratio","lipids","diabetes","case")
> parents_exercise <- c("education")
> parents_diet <- c("education")
> parents_smoking <- c("education")
> parents_alcohol <- c("education")
> parents_stress <- c("education")
> parents_high_blood_pressure <- c("education","exercise","diet",
        "smoking","alcohol","stress")
> parents_waist_hip_ratio <- c("education","exercise","diet",
        "smoking","alcohol","stress")
> parents_lipids <- c("education","exercise","diet",
        "smoking","alcohol","stress")
> parents_diabetes <- c("education","exercise","diet",
        "smoking","alcohol","stress","high_blood_pressure",
        "waist_hip_ratio","lipids")
> parents_case <- c("education","exercise","diet","smoking","alcohol","stress",
        "high_blood_pressure","waist_hip_ratio","lipids","diabetes")
> parent_list <- list(parents_exercise,parents_diet,parents_smoking,
    parents_alcohol,parents_stress,parents_high_blood_pressure,
       parents_waist_hip_ratio,parents_lipids,parents_diabetes,parents_case)
```

Again we can automatically specify models using the automatic_fit function which now will fit models for the extra variables specified in node_vec. Note that the risk factors lipids and waist_hip_ratio are continuous. We can allow nonlinear effects for these variables by using the spline_nodes argument, which fits 3 degree of freedom natural cubic splines as a default, as below:

```
> model_list=automatic_fit(data=stroke_reduced, parent_list=parent_list,
      node_vec=node_vec, prev=.0035,common="region*ns(age,df=5)+
      sex*ns(age,df=5)",spline_nodes = c("waist_hip_ratio","lipids","diet"))
```

Single sequential PAFs can be estimated using the function seq_paf, which has the same structure as joint_paf. The most important argument is riskfactor_vec, a vector of risk factors. The sequential PAF is estimated for the risk factor specified in the last position of riskfactor_vec conditional on the risk factors in earlier positions. For instance, the code below estimates the sequential PAF for eliminating diabetes, in a population where smoking and high_blood_pressure are already eliminated. As can be seen below, this estimator is randomised: the estimate will vary slightly over differing simulated data sets. The reason for this is that now the discrete variable diabetes is included in the dataset: $\mathbf{D}_{\{\text{smoking, high\_blood\_pressure}\}}$, and values for diabetes under interventions for smoking

and `high_blood_pressure` are randomly simulated. Nevertheless as demonstrated below, the variation over simulation repetitions is fairly minimal and this variability will be accounted for in the bootstrap confidence interval. Overall, this analysis suggests that in a population with no smoking and no high blood pressure, an extra 2.4% of strokes (taken as a percentage of the number of strokes in the current population) might be prevented if there was no diabetes.

```
> seq_paf(stroke_reduced,model_list,parent_list,node_vec,prev=0.0035,
          riskfactor_vec=c("smoking","high_blood_pressure","diabetes")
          ,nsim=1)


0.02382662


> seq_paf(stroke_reduced,model_list,parent_list,node_vec,prev=0.0035,
          riskfactor_vec=c("smoking","high_blood_pressure","diabetes")
          ,nsim=1)


0.02267426


> seq_paf(stroke_reduced,model_list,parent_list,node_vec,prev=0.0035,
          riskfactor_vec=c("smoking","high_blood_pressure","diabetes"),
          ci=TRUE,nsim=1)


                 est     bias debiased_est norm_lower norm_upper
sequential PAF 0.024 2.94e-05        0.024     0.0156     0.0323
```

Average PAF can be estimated using the function `average_paf`. The default estimation method is to first estimate the joint PAF for all possible risk factor subsets, $\mathbf{S}$ denoting a particular subset, next to estimate all possible sequential PAFs, $PAF_{j|\mathbf{S}}$, from the vector of joint PAFs and finally substitute these estimated sequential PAFs into (23). Recall that in estimating the joint PAF for the risk factor set $\mathbf{S}$, a data set $D_{\mathbf{S}}$ corresponding to this joint intervention is simulated recursively. The recursive nature of this simulation can be exploited to perform the estimation of all 2^K joint PAFs efficiently. For instance, when simulating data: $D_{\mathbf{S}\cup\{j\}}$ corresponding to eliminating risk factors: $\mathbf{S}\cup\{j\}$, with j being the final risk factor eliminated, data corresponding to eliminating the risk factors in $\mathbf{S}$, $D_{\mathbf{S}}$ has already been simulated. `average_paf` calculates the joint PAF for the 2^K risk factor subsets in an order that allows extensive use of this fact. As illustrated in the results below, the estimated average PAF is highest for `high_blood_pressure` at 0.259, with `smoking` at 0.106 and `diabetes` at 0.0395. These three quantities sum to the estimated joint PAF, 0.405, as expected. In addition, average sequential PAFs by elimination position for each risk factor is provided. Note that the sequential PAF for diabetes is most effected by elimination position. This makes sense based on its position in the causal graph (causally upstream of `smoking` and `high_blood_pressure`)

```
> out <- average_paf(stroke_reduced,model_list,parent_list,
node_vec,prev=0.0035,riskfactor_vec
=c("smoking","high_blood_pressure","diabetes"))
> print(out)
```

```
                 position         risk factor   estimate
1  elimination position 1             smoking 0.10530974
2  elimination position 2             smoking 0.10030958
3  elimination position 3             smoking 0.10349950
4  elimination position 1 high_blood_pressure 0.27667668
5  elimination position 2 high_blood_pressure 0.26135515
6  elimination position 3 high_blood_pressure 0.25422371
7  elimination position 1            diabetes 0.05407963
8  elimination position 2            diabetes 0.03472414
9  elimination position 3            diabetes 0.02355873
10                Average             smoking 0.10303961
11                Average high_blood_pressure 0.26408518
12                Average            diabetes 0.03745417
13                  Joint                     0.40457895
```

In the above analysis, the estimator is again randomised. This default estimation method for `average_paf` requires estimating $2^K - 1$ joint PAFs, each estimated joint PAF corresponds to a single simulated data set $D_{\mathbf{S}}$, the simulation of which can generate substantial Monte Carlo variability for small datasets when K is also small. As an alternative, by setting the argument `exact=FALSE`, one can sample `nperm` differing permutations of $\{1, ..., K\}$: corresponding to differing risk factor elimination orders, calculate sequential PAFs associated with each permutation and average the associated sequential PAF for a particular risk factor. For small K and `nperm` 2^K this alternative approach is likely to have reduced Monte Carlo error (compared to the 'exact' approach), despite some Monte Carlo error due to the sampling of permutations. Stratified sampling of permutations (so that the joint empirical distribution of permutation positions $\sigma(1), ..., \sigma(S)$ for some $S < K$ is uniform (as it would be if we calculated sequential PAFs for all $K!$ permutations), can help further reduce Monte Carlo error. For K risk factors, an integer multiple of $K(K-1)...(K-S+1)$ permutations are needed to implement such a strategy. Such stratified sampling of permutations is implemented through the argument `correct_order` (`correct_order`=S in the preceding example).

For larger K, the alternative approach of averaging sequential PAFs over a number of sampled permutations `nperm`$\approx 2^K$ or `nperm`$< 2^K$ may be less accurate than (22) due to the Monte Carlo error associated with sampling permutations, but may be more computationally feasable. When confidence intervals are not requested (`ci=FALSE`) an upper bound on the margin of error of the point estimate (in terms of how close to the calculation with `nperm` $= \infty$) is given (with 95%) confidence as calculated in Ferguson *et al.* (2018), provided permutations are sampled (using the argument `exact=FALSE`). Note that this margin of error assumes nonstrarstified sampling rather than the more accurate stratified sampling implemented here. The results below indicate that the three average PAFs are calculated to within an accuracy of 0.004 (with 95% confidence) compared to the exact estimate when `nperm` $\to \infty$.

```
> out <- average_paf(stroke_reduced,model_list,parent_list,node_vec,
prev=0.0035, riskfactor_vec=c("smoking","high_blood_pressure","diabetes"),
ci=FALSE,exact=FALSE, correct_order=2, nperm=60)
> print(out)
```

```
                position         risk factor   estimate Margin error lower bound Upper bound
1  elimination position 1             smoking 0.10441103 2.786493e-03  0.10162454  0.10719752
2  elimination position 2             smoking 0.10406168 1.177682e-03  0.10288399  0.10523936
3  elimination position 3             smoking 0.10349950 0.000000e+00  0.10349950  0.10349950
4  elimination position 1 high_blood_pressure 0.27582328 6.291276e-04  0.27519415  0.27645241
5  elimination position 2 high_blood_pressure 0.26066718 6.768796e-03  0.25389838  0.26743598
6  elimination position 3 high_blood_pressure 0.24764498 2.129574e-03  0.24551541  0.24977455
7  elimination position 1            diabetes 0.05407963 0.000000e+00  0.05407963  0.05407963
8  elimination position 2            diabetes 0.03942847 6.971034e-03  0.03245744  0.04639951
9  elimination position 3            diabetes 0.02412110 3.563301e-04  0.02376477  0.02447743
10               Average             smoking 0.10399074 9.525977e-04  0.10303814  0.10494333
11               Average high_blood_pressure 0.26137848 3.738582e-03  0.25763990  0.26511706
12               Average            diabetes 0.03920974 3.864373e-03  0.03534536  0.04307411
13                 Joint                     0.40457895 5.903706e-18  0.40457895  0.40457895
```

Of course, sampling error also needs to be accounted for when making a statement about estimation accuracy. While in this case with only $K = 3$ risk factors, estimation with 60 permutations should give a slightly more accurate point estimate for the average PAF compared to using equation (22) directly, the approximation error in both cases is much smaller than the sampling error. In fact, confidence intervals suggest comparable accuracy of using equation (22) (`full_results_a`) and calculating the average PAF using 60 sampled permutations with stratified sampling (`full_results_b`).

```
> full_results_a <- average_paf(stroke_reduced,model_list,parent_list,
node_vec,prev=0.0035,riskfactor_vec=c("smoking","high_blood_pressure",
"diabetes"), ci=TRUE)
> print(full_results_a)
```

```
                position         risk factor    est      bias debiased_est norm_lower norm_upper
1  elimination position 1             smoking 0.1100 -0.002300       0.1130     0.0918     0.1330
2  elimination position 2             smoking 0.1060  0.000482       0.1050     0.0892     0.1210
3  elimination position 3             smoking 0.1030  0.000395       0.1030     0.0890     0.1170
4  elimination position 1 high_blood_pressure 0.2750 -0.001090       0.2760     0.2570     0.2960
5  elimination position 2 high_blood_pressure 0.2580 -0.000116       0.2590     0.2360     0.2810
6  elimination position 3 high_blood_pressure 0.2440 -0.002010       0.2460     0.2180     0.2740
7  elimination position 1            diabetes 0.0541  0.000731       0.0533     0.0354     0.0713
8  elimination position 2            diabetes 0.0379  0.001700       0.0362     0.0203     0.0522
9  elimination position 3            diabetes 0.0244 -0.000195       0.0246     0.0153     0.0339
10               Average             smoking 0.1060 -0.000475       0.1070     0.0916     0.1220
11               Average high_blood_pressure 0.2590 -0.001070       0.2600     0.2380     0.2830
12               Average            diabetes 0.0388  0.000746       0.0381     0.0243     0.0518
13                 Joint                 PAF 0.4050 -0.000801       0.4050     0.3790     0.4320
```

```
> full_results_b <- average_paf(stroke_reduced,model_list,parent_list,
node_vec,prev=0.0035,riskfactor_vec=c("smoking","high_blood_pressure",
"diabetes"),ci=TRUE,exact=FALSE,
     correct_order=2, nperm=60)
```

	position	risk factor	est	bias	debiased_est	norm_lower	norm_upper
1	elimination position 1	smoking	0.1040	9.29e-04	0.1030	0.0815	0.1250
2	elimination position 2	smoking	0.1040	5.65e-04	0.1040	0.0862	0.1210
3	elimination position 3	smoking	0.1030	2.37e-05	0.1030	0.0881	0.1190
4	elimination position 1	high_blood_pressure	0.2760	4.34e-05	0.2760	0.2550	0.2970
5	elimination position 2	high_blood_pressure	0.2620	-3.45e-04	0.2620	0.2400	0.2840
6	elimination position 3	high_blood_pressure	0.2460	-2.25e-04	0.2460	0.2230	0.2690
7	elimination position 1	diabetes	0.0541	6.78e-04	0.0534	0.0371	0.0697
8	elimination position 2	diabetes	0.0396	3.95e-04	0.0392	0.0261	0.0522
9	elimination position 3	diabetes	0.0242	7.41e-05	0.0241	0.0155	0.0327
10	Average	smoking	0.1040	5.06e-04	0.1040	0.0855	0.1220
11	Average	high_blood_pressure	0.2610	-1.76e-04	0.2610	0.2400	0.2830
12	Average	diabetes	0.0393	3.82e-04	0.0389	0.0263	0.0515
13	Joint	PAF	0.4050	7.13e-04	0.4040	0.3770	0.4310

Results (estimated average PAFs and sequential PAFs by elimination position, along with associated variability bands) can be plotted over differing risk factors using `plot(full_results_b,number_rows=` and are displayed in Figure 7, the arguments `number_rows` and `max_PAF` controlling the number of rows to plot and the maximum value on the y-axis on each plot.

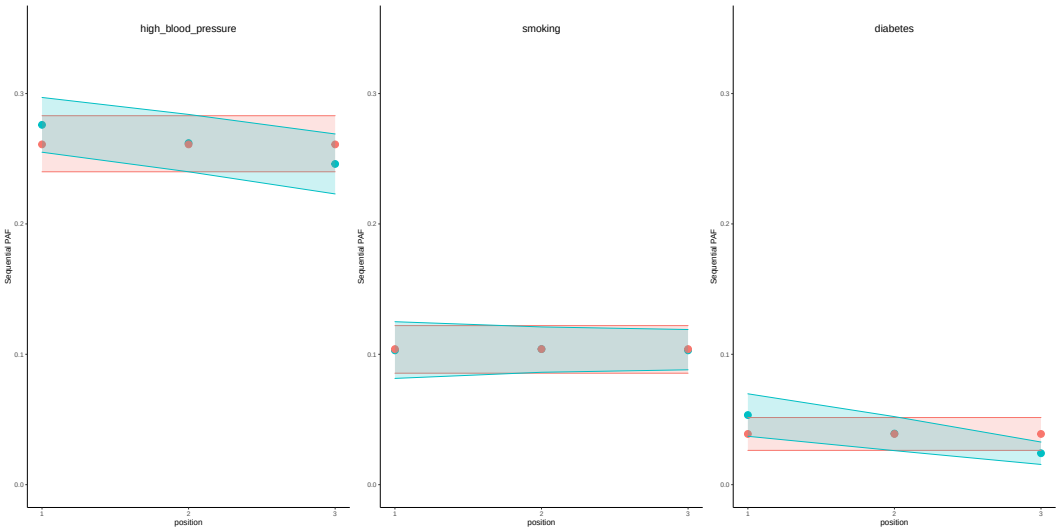


Figure 7: Estimated average PAFs and sequential PAFs for the group of risk factors: smoking, blood pressure and diabetes. Risk factors are plotted in decreasing order of estimated average PAF. Estimated average PAFs are shaded in pink, and estimated average sequential PAFs for each elimination position (with the averaging over differing configurations of risk factors eliminated prior to the risk factor under consideration) in blue. One expects sequential PAFs to decrease as elimination position increases as observed for blood pressure and diabetes.

Note that if `exact=`FALSE'` and `ci=`FALSE'`, the plotted variability bands will not be interpretable as confidence intervals, but rather as bands for the degree of possibility approximation error in the point estimate.

6.3. Computational considerations

As described here, `graphPAF`, facilitates incorporation of causal structure into estimation of joint, sequential and average PAFs, essentially by utilising recursive simulation methods based on an assumed causal structure. Ignoring such causal structure, as other approaches have in the past (for example, Rückinger, von Kries, and Toschke (2009), Ferguson *et al.* (2018)) may lead to bias. A drawback of this simulation based strategy is computational cost. Techniques such as bootstrap parallelization (through the `boot` library), intelligent ordering of calculations when calculating joint PAFs for differing risk factor subsets, stratified sampling of permutations when the number of risk factors is large and the use of the more efficient formula for average PAFs (23) can somewhat reduce these computational requirements. Computational cost depends jointly the size of the Bayesian networks and the size of the underlying dataset. The dataset `stroke_reduced` used in this manuscript has 13,712 rows and the algorithms described here can be run in reasonable time on most modern laptops when using this data. For larger datasets, splitting the complete dataset into independent subsets and running the methods independently on each subset before averaging might be recommended to avoid memory management problems.

7. Conclusions

In addition to implementing standard PAF estimation, `graphPAF` collates many recently developed tools for estimation of disease burden in nonstandard settings into one package. We hope it will be useful to statisticians and epidemiologists who are interested in comparisons of disease burden over multiple risk factors, both discrete and continuous.

Statements and Declarations

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