Appendix to:
Heterogeneity in Coronary Heart Disease Risk

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The existence of latent factors L has impact on the age dependence of observed survival and hazard functions (1). To study this impact, we explicitly write the dependence of the conditional hazard λ on age a and observed risk factors r:

$$\lambda(a, r|L) = \lambda(a, r)\, e^L$$

The corresponding conditional survival is given by

$$S(a, r|L) = \exp\left(-e^L \int_0^a \lambda(t, r)\, dt\right) \tag{Eq. A.1}$$

Survival is reduced for large cumulative $\lambda(a, r)$ and for large frailty e^L. For given age and observed risk factors, individual differences in survival are stronger for broad distribution of the frailty e^L. The depletion of high-risk individuals is reflected in the marginal hazard by inclusion of the conditional survival in the expectation value:

$$\bar{\lambda}(a, r) = \frac{E[\lambda(a, r|L)\, S(a, r|L)]}{E[S(a, r|L)]} = \lambda(a, r) \frac{E[\exp(L)\, S(a, r|L)]}{E[S(a, r|L)]} \tag{Eq. A.2}$$

As the contribution of individuals with high frailty e^L diminishes, the marginal hazard attenuates with age, i.e. $\bar{\lambda}(a, r)/\lambda(a, r)$ decreases with age. The attenuation is stronger for larger λ, see Eq. A.1. Therefore, also HRs comparing different levels of risk factors r_1, r_2, attenuate:

$$\frac{\bar{\lambda}(a, r_1)}{\bar{\lambda}(a, r_2)} = \frac{\lambda(a, r_1)}{\lambda(a, r_2)} \frac{E[\exp(L)\, S(a, r_1|L)]}{E[\exp(L)\, S(a, r_2|L)]} \frac{E[S(a, r_2|L)]}{E[S(a, r_1|L)]} \tag{Eq. A.3}$$

This means for $\frac{\bar{\lambda}(a, r_1)}{\bar{\lambda}(a, r_2)} > 1$, this fraction to become smaller than $\frac{\lambda(a, r_1)}{\lambda(a, r_2)}$ with advancing age. The conditional HR $\lambda(a, r_1)/\lambda(a, r_2)$ represents the HR for two individuals that differ only in the level r_1 vs. r_2 of some risk factor(s). In contrast, the marginal HR applies to groups with levels r_1 vs. r_2. Because hazards cannot be determined for individuals, only the marginal hazard and the marginal HR can directly be deduced from incidence data.

References

1.   Balan TA, Putter H. A tutorial on frailty models. Stat Methods Med Res. 2020;29(11):3424-54.