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Estimates of familial risks from family data are biased when ascertainment of families is not independent of family history: Author's response

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Authors' response

Patients with hyperplastic polyposis syndrome (HPS) harbour multiple colorectal hyperplastic polyps and are at risk of developing colorectal cancer (CRC).^{1–6} In a recent study we determined the RR of CRC (5.4; 95% CI 3.7 to 7.8) and HPS (39; 95% CI 13 to 121) in first-degree relatives (FDRs) of patients with HPS compared with the general population.⁷ Win *et al* raised concerns that probands in our study might have been 'preferentially ascertained because of a known family history (to any degree of genetic relatedness) of CRC' which would lead to an ascertainment bias. This would then overestimate the familial risk of CRC.

As discussed in the original paper, the majority of probands included in our cohort were symptomatic and thus did not encompass preferentially ascertained individuals with a known family history of CRC. At closer analysis, only 3/57 probands (5%) presented at our clinic because of a positive family history of CRC and none had a known family history of HPS. If these probands and their FDRs (n=19) were excluded and the data reanalysed, the RR of CRC in FDRs would become 5.0 (95% CI 3.3 to 7.4), which is only marginally lower than the original estimate. However, because we included all probands satisfying the criteria for HPS irrespective of the reason for presentation, we believe ascertainment was in fact independent of family history.

Besides the bias risk mentioned by Win *et al*, other potential biases should be taken into consideration. First, the majority of probands included in this study were diagnosed because they were symptomatic and thus represent a selected population. HPS is a condition with an unknown underlying genetic defect and a heterogeneous phenotype. Consequently, different levels of disease severity and corresponding familial risks may exist in HPS. It is possible that the largely symptomatic probands in our study represent an HPS phenotype that is more aggressive and holds a higher risk of familial involvement than other (unidentified) HPS cases that are asymptomatic. Therefore, our findings concerning familial risk cannot by default be extrapolated to all cases of HPS. In addition to patients with symptomatic HPS identified in a clinical setting, a large cohort of asymptomatic patients with HPS derived from a population-based colonoscopy screening programme would be useful to adequately deal with this selection bias.

Second, it was presumed in our study that more colonoscopies were performed in FDRs in response to a diagnosis of CRC in probands. This would lead to higher frequencies of colonoscopies in FDRs than in the general population, possibly leading to more diagnoses. To avoid this bias we did not use follow-up data from FDRs after the time of diagnosis of CRC in a proband (censoring). It is still possible that more colonoscopies have been performed in FDRs as a result of HPS diagnosis in the absence of CRC in the proband, although a diagnosis of HPS in the time frame of our study was not considered an indication for colonoscopic screening of relatives.

As an alternative for familial CRC analysis, Win *et al* suggest comparing family histories of patients with HPS and non-HPS patients who, as a whole, had the same a priori risk of being diagnosed with HPS. In our opinion, an ideal study would be to perform colonoscopic screening in all FDRs of patients with HPS as well as in an age- and gender-matched control group from the general population. Such data may become available from large-scale colonoscopic screening studies.

In all, we were well aware of the potential biases that could have inflated our estimates of RR and accordingly applied various measures to avoid these. We therefore believe that our study provides a fair representation of patients with HPS, their FDRs and the associated familial risk of CRC in a clinical setting.

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Analysis of deaths occurring within the Nottingham trial of faecal occult blood screening for colorectal cancer

We read with interest the analysis of deaths occurring within the Nottingham trial of faecal occult blood screening for colorectal cancer performed by Whynes and colleagues,¹ reported in a recent issue of *Gut*. While the aims of this study are to be commended, we have some concerns regarding the interpretation of ages at death and the methodology used to assign deprivation score.

With respect to age at death, 'those who participated in screening died at a more advanced age than the controls who, in turn, enjoyed a longer lifespan than non-participants.' One interpretation that is consistent with this finding is that, among the intervention group, those who lived longer were more likely to participate in screening and those who died youngest were less likely to participate in screening.

In assigning a deprivation score to each trial participant based solely on the Index of Multiple Deprivation of the address of their corresponding general practice Whynes *et al* make two broad assumptions. First, they assume that the level of deprivation experienced by the population in which the general practice building is located reflects the level of deprivation experienced by the registered practice population itself. Second, they assume that the general practice deprivation score adequately reflects the deprivation experience of individuals who participated in the Nottingham trial. The second assumption is an inherent problem with area-based measures of deprivation, which is that they assume that all individuals have the socio-economic characteristics of the area in which they live. The first assumption, however, may invalidate the Index of Multiple Deprivation as it is used in the study. McLean *et al*² found that analyses that employed this methodology significantly underestimated the relationship between deprivation and ill health. This might be due to general practice populations being distributed over large geographical areas that may not reflect the location of the GP surgery. Additionally, general practices may be located in areas significantly different to the areas in which registered patients live. Thus, the validity of these assumptions remains questionable and thus the relative contribution of socioeconomic circumstances on these results becomes less certain.

Therefore, the interpretation of age at death within each of the trial arms,

Authors' response

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