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Title **The Causes and Effects of Socio-Demographic Exclusions from Clinical Trials**

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Aim

To investigate the causes and effects of excluding women, older people, and ethnic groups from clinical trials, focusing on two drugs, statins and NSAIDs (non steroidal anti-inflammatory drugs).

Conclusions and results

Excluding people from clinical trials who are likely to need, or benefit from, the intervention could compromise the external validity (generalizability) of clinical trials.

1. In the USA the discourse includes equitable access of different groups. The UK debate is limited.
2. Trial populations: *Statins:* Average age of trial participants was 58.5 years, only 16.3% were women. Statins reduced CVD incidence by about 25% in men and women. Older people up to 75 years also benefited. *NSAIDs:* Average age was 61.9 years, and women were well represented (68.5%). Ethnicity was not well reported for either drug.
3. Drug utilization. *Statins:* Used to treat 23% of the cohort. Statin users were younger than non-statin users and had superior outcomes. *NSAIDs:* High current exposure to NSAIDs increased the risk for GI side effects and renal impairment. Side-effect risk increased with age, being female diminished risk.
4. Population in need. *Statins:* An estimated 537 000 CVD cases would qualify for statins in England per year. Women constitute 45% of this population, two thirds being 65+. Need varies by ethnic group. No sex bias in prescribing was found, but use was more common in younger people. *NSAIDs:* 6.3% of adults aged 35+ reported hip and/or knee pain associated with OA. 3.9% of adults used prescribed analgesics; they were more likely to be women and older (65+).
5. The mismatch: *Statins:* Women formed half the "with need" and "on treatment" populations, but were markedly under-represented in trials. Those aged 65+ formed nearly two thirds of the "with need" population, but only one fifth of trial samples, and were less likely to be treated than younger subjects. *NSAIDs:* Women formed two thirds of trial samples, the "with need", and "on treatment" populations. People aged 65+ formed three fifths of the "on treatment" population, but were under-represented in trials.
6. Meta-analysis might overcome problems of low inclusion in assessing relative effectiveness, but assessing side effects in different groups would require massive trials. Measures of absolute effectiveness are vital to analyze benefit, harm, and cost effectiveness. Measurements involving underlying risk levels will be severely biased if population groups are not adequately represented.

Recommendations

Exclusion from trials of women, older people, and ethnic minorities has been a relatively neglected issue in the UK, and there is confusion about diversity issues. Under-representation occurs, but in drug trials it may not always affect the external validity of relative effect estimates. Measures of absolute effectiveness, absolute harm, and cost effectiveness are associated with different underlying risk levels in different sociodemographic groups, and under-representation will bias absolute effect estimates. The complexity of the issues made development of a single, comprehensive theoretical model impossible.

Methods

See Executive Summary link above.

Further research/reviews required

- Multidisciplinary assessment of realistic options for trialists to address the issue of exclusion
- Clarify the use of ethnic categories in health research, and the implications of different dimensions of aging and sex/gender
- Identify barriers and facilitators to the involvement of different population groups in research
- Further investigate the susceptibility of men to NSAID adverse events
- Develop a "register of registries and databases" and explore how to improve linked health information systems in the UK.

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