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Need to combine individual strategies with population-level strategies in the prevention of coronary heart disease

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ABSTRACT
INTRODUCTION: The aim of this paper is to examine the relation between the distribution of risk, the distribution of coronary heart disease (CHD) events and the proportion who develop CHD according to risk.

MATERIAL AND METHODS: Baseline data from a cross-sectional study conducted in 1999-2001 comprising information on systolic blood pressure, low density lipoprotein cholesterol and a multifactor risk score, The Copenhagen Risk Score, were related to ten years of fatal and non-fatal events of CHD in 6,784 participants.

RESULTS: The results were unambiguous regarding all three examined parameters. They showed that the majority of all fatal and non-fatal events of CHD occur within the large group of the population which is at low or no risk of CHD.

DISCUSSION: The three determinants in relation to CHD events indicate that changing the risk of a whole population through widespread comprehensive societal policies may be more efficient than medical treatment and health counselling targeting persons already at high-risk, which will be of benefit for the individual persons only.

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TRIAL REGISTRATION: Inter99 is registered with ClinTrials. Gov as no. NCT00289237.
Distribution of variables for all participants, and participants who develop coronary heart disease during a ten-year period.

<table>
<thead>
<tr>
<th>Variable/characteristic</th>
<th>All participants</th>
<th>Participants who develop CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean (± SD)</td>
<td>45.8 (± 9.06)</td>
<td>51.1 (± 7.73)</td>
</tr>
<tr>
<td>Gender, male, %</td>
<td>48.2</td>
<td>63.7</td>
</tr>
<tr>
<td>SBP, mmHg, mean (± SD)</td>
<td>128 (± 16.06)</td>
<td>135 (± 17.06)</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/l, mean (± SD)</td>
<td>3.5 (± 0.96)</td>
<td>3.9 (± 1.07)</td>
</tr>
<tr>
<td>CRS, mean (± SD)</td>
<td>3.5 (± 4.65)</td>
<td>8.3 (± 9.55)</td>
</tr>
<tr>
<td>Sample size/events, n</td>
<td>6,656-6,783</td>
<td>430-444</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; CRS = Copenhagen Risk Score; LDL = low density lipoprotein; SBP = systolic blood pressure; SD = standard deviation.

a) Sample size differs between risk factors: SBP = 6,783, LDL cholesterol = 6,656, CRS = 6,733.
b) Events of CHD differ between risk factors: SBP = 444, LDL cholesterol = 430, CRS = 441.

Population
A random sample of 13,016 persons aged 30-60 years was drawn from the south-western part of the Copenhagen county, Denmark. A total of 82 persons were non-eligible (dead or untraceable), and among the 6,906 persons who attended, 122 were excluded due to alcoholism, drug abuse or linguistic problems [11]. This left 6,784 (52.5%) for analysis.

The participants had fasting blood samples taken. The samples were stored in a freezer at -18°C and sent to the laboratory at Steno Diabetes Centre for analysis on a daily basis. Total cholesterol, triglycerides and high-density lipoprotein (HDL) cholesterol were determined with enzymatic techniques (Boerhinger Mannheim, Germany). LDL cholesterol was calculated by Friedewald’s equation. SBP was measured twice with a mercury sphygmomanometer after five minutes of rest in the supine position. The average of the two measurements was used for analysis [11]. The CRS is a risk score that assesses a person’s absolute risk of CHD within the next ten years [12]. The CRS is based on non-modifiable factors such as age, height, previous myocardial infarction (self-reported), diabetes (self-reported) and family history of CHD (self-reported), and modifiable factors like smoking, cholesterol, weight and systolic blood pressure.

The end-points were fatal and non-fatal CHD (International Classification of Diseases (ICD) 10: I20-125) during a ten-year period. End-point data were retrieved from the Danish National Patient Register and the Danish Register of Causes of Death [13, 14]. The distribution of LDL cholesterol, SBP and CRS data were compared with data on the risk of CHD and CHD events during a ten-year follow-up period. These comparisons make it possible to investigate the relationship between persons at high risk of developing CHD, on the one hand, and fatal and non-fatal events of CHD during the follow-up period on the other hand. During the ten years of follow-up, 444 persons had a CHD event (Table 1).

**Statistical analysis**
Among the 6,784 persons included in the final sample for analysis, we obtained SBP data on 6,783 persons, LDL cholesterol data on 6,656 persons and CRS data on 6,733 persons [11].

Data analyses were performed using the SAS Proc Mixed procedures (SAS Statistical Software V.9.3; SAS Institute, Cary, North Carolina, USA) to determine the distribution of both baseline data and end-points. All analyses were stratified by both sex and age, but neither sex nor age deviated significantly, and the stratified data are therefore not presented in this paper.

**Trial registration:** Inter99 is registered with ClinTrials. Gov as no. NCT00289237.

**RESULTS**
Data confirm that there is a clear increase in the proportion which develops CHD in the face of an increased risk of SBP and LDL cholesterol and an increased total risk as assessed by the CRS (illustrated in Figure 1, Figure 2 and Figure 3). The increase is 3.8-13% for SBP, 4.2-33.3% for LDL cholesterol and 3.8-66.7% for CRS.

The number of events (CHD) was higher in the proportion of the population that has a low or no risk, which is larger than the proportion of the population that is at high risk. For SBP, more than half of the events occurred in the group with no hypertension and less than 10% occurred in those with second or third degree hypertension. For LDL cholesterol, nearly a quarter of the events occurred among those whose LDL cholesterol was below 3 mmol/l, and slightly more than 10% among those with an LDL cholesterol of 5 mmol/l or more. Finally, for CRS more than 75% of the events occurred within the group of people having a CRS between low and five, while less than 10% occurred in persons having a CRS above 20.

**DISCUSSION**
The present study illustrates that most CHD events occur in the vast majority of persons who have no or a relative low risk of CHD. Thus, only a minor proportion of those facing an event are at high risk.

These findings are in accordance with those reported from a similar observational study from Sweden in the 1970s [10] and with those of a simulation study carried out by Cooney et al [3]. The latter challenges the traditional high-risk strategy in preventive cardiology as the only approach to the worldwide threat of CHD.
lack of effect of multifactorial population-level interventions [15]. Thus, the majority of future cases cannot be reached by a high-risk strategy. This is in accordance with the emerging literature on population-level changes in preventing CHD [2] which show major population-level effects of small changes introduced at societal level [9]. These data support the core of Rose’s Prevention Paradox which states that a small shift in the risk of disease across a whole population can lead to a greater reduction in disease burden than a large shift among those persons already at high risk; the latter approach does not address the causes of the problem [3, 6, 8, 9, 16].

An important question is at which level of the various determinants a high-risk approach should be initiated. The pertinence of this question lies in the logistic problems that may arise if a large proportion of the population is included. Following the official European guidelines [7], the proportion of the population to be included differs according to the different determinants. Thus, using LDL cholesterol as the parameter, two thirds of the population is included in the high-risk group (above 3 mmol/l). A systolic blood pressure above 140 mmHg would include only one quarter of the population in the high-risk group, and a CRS above 10% would include only 5%. The latter is not entirely in line with the recommendations from the official guidelines [7] which deal only with the risk of fatal events and not total events, but 10% total events is comparable with 5% fatal events [17]. The fact that a considerable proportion of the population has LDL levels above the recommended level indicates that the sole use of a high-risk strategy is not feasible. In daily practice, medical treatment and health counselling can be provided only to a limited number of persons, viz. those at high risk, and not for the vast majority of the population. For some persons, medical treatment is obviously needed because they are at high risk of CHD [2, 3, 7]. Several attempts have been made to improve risk stratification, even resort to gene analysis, but no study has yet shown a substantially improved method for discrimination between population groups at risk for CHD. Nor has it been shown whether such stratification would lead to a more efficient high-risk strategy.

Another problem with the high-risk strategy is that we need to identify those who are at risk. Nearly half of those who are invited to participate in the study did not accept the invitation. A declining trend in participation rate is seen all over the world and there seems to be no
good solutions to arrest this trend. This has serious implications for the high-risk strategy, as we know that non-responders have a higher mortality and a higher prevalence of risk factors [18] and more often belong to the lower social classes [19]. The implication of this is that a higher proportion of the population should potentially be classified as belonging to the high-risk group and should therefore receive health counselling or medical treatment, but because these non-responders do not turn up, they cannot be reached by a high-risk strategy.

They may, however, potentially benefit from population-level strategies (e.g. taxation) [2], which do not necessarily involve personal initiative which could be a further argument for using the population-level strategy. This supports Rose’s suggestion and interpretations of the two approaches: A population-level strategy should be used to reduce the burden of disease to the benefit of society, whereas a high-risk strategy should be reserved for treatment to help the individual citizen.

The present study has strengths and limitations that must be addressed. Inter99 is a methodologically well-executed study where complete register-based follow-up on morbidity and mortality contribute as a major strength. The population-sample is large, yet it could be argued that the lack of young persons below 30 years of age is a limit, because the study provides no data about the early life of the population.

CONCLUSION
To conclude, the present study supports prior scientific publications and emerging literature arguing that structural prevention strategies are conceivably more effective than high-risk strategies in curbing the prevalence of CHD. Still, as those at high risk will not necessarily benefit solely from a population-level strategy, society would benefit most from a combination of both approaches.

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LITERATURE