Integrating the Effect of Polygenic Scores, Low Density Lipoproteins and Systolic Blood Pressure on the Lifetime Risk of Cardiovascular Disease

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Background

Polygenic score (PGS) predicts lifetime risk of CAD

LDL and SBP have cumulative effects on lifetime risk of CAD


Objectives

• **Objective**: to evaluate how much lifetime risk of cardiovascular disease varies at all levels of a polygenic score (PGS) for CAD depending on differences in lifetime exposure to low-density lipoproteins (LDL) and systolic blood pressure (SBP)

  • To make inferences about how a PGS for CAD can be combined with information about LDL and SBP - which are modifiable and the current targets of therapy to reduce risk
  • To directly inform individual screening and treatment decisions
  • To provide a potential framework for incorporating PGS for CAD into clinical medicine
Study population and primary outcomes

• **Study Population:** 445,566 participants enrolled in the UK Biobank
  • 54% females
  • Mean age at enrolment: 57.2 years (mean age at last follow-up 65.2 years)
  • Mean LDL-C: 138 mg/dl (mean apoB level: 104.4 mg/dL)
  • Mean SBP: 137.8 mmHg

• **Primary Outcomes:** Major coronary events (MCE); N = 23,032
  • First occurrence of fatal or non-fatal myocardial infarction, or coronary revascularization

• **Primary Analysis:** time to event analysis
  • Age as the time scale
  • Participants censored at age of the first occurrence of a primary outcome event, death due to a cause other than myocardial infarction (as a competing risk), or end of follow-up
Construction of genetic scores

- **6,595,830 variants**
  - Prune variants in very high LD ($r^2 > 0.9$) to optimize PGS
  - **PGS: 4,051,820 variants**

Exclude variants associated with LDL or SBP at $p < 5 \times 10^{-8}$ to construct LDL and SBP MR instruments

- **8,056 variants associated with LDL at $p < 5 \times 10^{-8}$**
  - Further prune for LD to construct optimal instrument for Mendelian randomization
  - **100 variants associated with LDL at $p < 5 \times 10^{-8}$**
    - Align variants to LDL effect size
    - **LDL genetic instrument**
      - Analysis: Mendelian randomization (CAD ES per unit Δ LDL)

- **5,939 variants associated with SBP at $p < 5 \times 10^{-8}$**
  - Further prune for LD to construct optimal instrument for Mendelian randomization
  - **61 variants associated with SBP at $p < 5 \times 10^{-8}$**
    - Align variants to SBP effect size
    - **SBP genetic instrument**
      - Analysis: Mendelian randomization (CAD ES per unit Δ SBP)

- **4,037,825 (99.7%) remaining variants**
  - Align variants to CAD effect size
  - **PGS for CAD**
    - Analysis: Genetic Association study (CAD ES per SD Δ PGS)
### Associations of polygenic score with major coronary events

#### Polygenic score for CAD

<table>
<thead>
<tr>
<th>Participants</th>
<th>PGS</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. participants</td>
<td>445,566</td>
<td>89,121</td>
<td>89,128</td>
<td>89,114</td>
<td>89,105</td>
<td>89,098</td>
</tr>
<tr>
<td>No. events</td>
<td>23,032</td>
<td>2,791</td>
<td>3,618</td>
<td>4,466</td>
<td>4,990</td>
<td>7,167</td>
</tr>
<tr>
<td>Risk (%)</td>
<td>5.2</td>
<td>3.1</td>
<td>4.1</td>
<td>5.0</td>
<td>5.6</td>
<td>8.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.45 (1.43-1.47)*</td>
<td>reference</td>
<td>1.31 (1.25-1.38)</td>
<td>1.63 (1.56-1.71)</td>
<td>1.85 (1.76-1.93)</td>
<td>2.77 (2.65-2.89)</td>
</tr>
</tbody>
</table>

#### Men

<table>
<thead>
<tr>
<th>Participants</th>
<th>PGS</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. participants</td>
<td>203,545</td>
<td>40,576</td>
<td>40,728</td>
<td>41,040</td>
<td>40,814</td>
<td>40,387</td>
</tr>
<tr>
<td>No. events</td>
<td>17,783</td>
<td>2,137</td>
<td>2,829</td>
<td>3,497</td>
<td>3,857</td>
<td>5,463</td>
</tr>
<tr>
<td>Risk (%)</td>
<td>8.7</td>
<td>5.3</td>
<td>6.9</td>
<td>8.5</td>
<td>9.4</td>
<td>13.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.44 (1.42-1.46)*</td>
<td>reference</td>
<td>1.34 (1.26-1.41)</td>
<td>1.66 (1.56-1.71)</td>
<td>1.87 (1.76-1.93)</td>
<td>2.78 (2.65-2.89)</td>
</tr>
</tbody>
</table>

#### Women

<table>
<thead>
<tr>
<th>Participants</th>
<th>PGS</th>
<th>Quintile 1</th>
<th>Quintile 2</th>
<th>Quintile 3</th>
<th>Quintile 4</th>
<th>Quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. participants</td>
<td>242,021</td>
<td>48,545</td>
<td>48,400</td>
<td>48,074</td>
<td>48,291</td>
<td>48,711</td>
</tr>
<tr>
<td>No. events</td>
<td>5,249</td>
<td>654</td>
<td>789</td>
<td>969</td>
<td>1,133</td>
<td>1,704</td>
</tr>
<tr>
<td>Risk (%)</td>
<td>2.2</td>
<td>1.4</td>
<td>1.6</td>
<td>2.0</td>
<td>2.4</td>
<td>3.5</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.46 (1.42-1.50)*</td>
<td>reference</td>
<td>1.22 (1.10-1.36)</td>
<td>1.52 (1.37-1.68)</td>
<td>1.76 (1.60-1.94)</td>
<td>2.70 (2.46-2.94)</td>
</tr>
</tbody>
</table>

* Per 1 SD increase in PGS
Trajectories of cardiovascular risk by PGS

Cumulative lifetime risk of major coronary events (%) vs Age (years)

- Highest PGS quintile
- Middle PGS quintile
- Lowest PGS quintile

[Graph showing the cumulative lifetime risk of major coronary events across different age groups for the highest, middle, and lowest PGS quintiles.]
Changes in PGS trajectories of cardiovascular risk by LDL and SBP
Lifetime risk of MCE to age 75 by PGS, LDL and SBP

Variation in lifetime risk of MCE within each decile of PGS depending on lifetime exposure to LDL and SBP

(Mendelian randomization analyses)
Lifetime risk of MCE to age 75 by PGS, LDL and SBP

Variation in lifetime risk of MCE within each decile of PGS depending on lifetime exposure to LDL and SBP
(Mendelian randomization analyses)
Mendelian randomization analysis of lifetime risk

Observational cohort analysis of short-term risk

Participants in LOWEST PGS quintile with high LDL and SBP had higher risk compared to participants in HIGHEST PGS quintile with low LDL and SBP (p < 0.001)
# Expected clinical benefit of lipid lowering on risk of MCE

## Mendelian randomization analysis of lifetime risk

Expected **ARR (%)** in lifetime risk from lowering LDL by 30% assuming RRR of 20% per mmol lower LDL

<table>
<thead>
<tr>
<th>PGS quintile 1</th>
<th>PGS quintile 2</th>
<th>PGS quintile 3</th>
<th>PGS quintile 4</th>
<th>PGS quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>+1 mmol LDL &amp; 10 mmHg</td>
<td>5.32</td>
<td>6.61</td>
<td>8.26</td>
<td>9.54</td>
</tr>
<tr>
<td>+0.5 mmol LDL &amp; 5 mmHg</td>
<td>2.61</td>
<td>3.28</td>
<td>4.10</td>
<td>4.53</td>
</tr>
<tr>
<td>Pop. mean LDL &amp; SBP</td>
<td>1.26</td>
<td>1.61</td>
<td>2.01</td>
<td>2.39</td>
</tr>
<tr>
<td>-0.5 mmol LDL &amp; 5 mmHg</td>
<td>0.60</td>
<td>0.77</td>
<td>0.96</td>
<td>1.06</td>
</tr>
<tr>
<td>-1 mmol LDL &amp; 10 mmHg</td>
<td>0.28</td>
<td>0.36</td>
<td>0.45</td>
<td>0.53</td>
</tr>
</tbody>
</table>


## Observational cohort analysis of short-term risk

Expected **ARR (%)** in short-term risk from lowering LDL by 30% assuming RRR of 20% per mmol lower LDL

<table>
<thead>
<tr>
<th>PGS quintile 1</th>
<th>PGS quintile 2</th>
<th>PGS quintile 3</th>
<th>PGS quintile 4</th>
<th>PGS quintile 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed data Measured LDL &amp; SBP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL 185 mg/dl &amp; SBP 151 mmHg</td>
<td>0.69</td>
<td>0.82</td>
<td>0.96</td>
<td>1.03</td>
</tr>
<tr>
<td>LDL 163 mg/dl &amp; SBP 144 mmHg</td>
<td>0.38</td>
<td>0.51</td>
<td>0.59</td>
<td>0.67</td>
</tr>
<tr>
<td>LDL 144 mg/dl &amp; SBP 136 mmHg</td>
<td>0.27</td>
<td>0.32</td>
<td>0.42</td>
<td>0.39</td>
</tr>
<tr>
<td>LDL 125 mg/dl &amp; SBP 127 mmHg</td>
<td>0.15</td>
<td>0.17</td>
<td>0.23</td>
<td>0.26</td>
</tr>
<tr>
<td>LDL 105 mg/dl &amp; SBP 120 mmHg</td>
<td>0.11</td>
<td>0.10</td>
<td>0.12</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Less expected clinical benefit | More expected clinical benefit

Observational prospective cohort analysis of risk of incident major coronary events among participants not on lipid lowering therapy at baseline; divided into groups with 1 SD higher/lower LDL and SBP compared to mean
Sensitivity analyses

- **Sensitivity analyses**: results essentially unchanged with the same “pattern” of results for:
  - Men and women (*with different absolute rates of disease*)
  - Mendelian randomization analyses of lifetime risk, and observational data analyses of short-term risk (*with different absolute rates of disease*)
  - Multiple methods for constructing PGS for CAD
    - External weighting by CARDIoGRAMplusC4D effect size estimates
    - Ldpred
    - metaGRS
  - Regardless of number variants included in the PGS for CAD
    - Including scores composed of 1,800, 1.7M, 4.1M or 6.6M genetic variants
Conclusions

• Lifetime risk of cardiovascular disease varies substantially at all levels of a polygenic score for CAD depending on differences in lifetime exposure to LDL and SBP

• Therefore, combining information about lifetime exposure to LDL and SBP with a PGS for CAD should more accurately estimate lifetime risk of cardiovascular disease, more accurately identify persons who may benefit from early interventions to reduce risk, and better estimate the potential benefit from early interventions
  • Because absolute lifetime risk of cardiovascular disease depends on PGS and lifetime exposure to LDL and SBP
  • And, clinical benefit depends on BOTH absolute risk (which depends on PGS as well as LDL and SBP) & the absolute reduction in LDL or SBP achieved with treatment (which depends on baseline LDL and SBP levels)
  • When combined with LDL and SBP, a PGS for CAD has the potential to help personalize the prevention of cardiovascular disease by helping to identify persons who may benefit the most from early interventions to minimize the cumulative effects of lifetime exposure to LDL and SBP
One more thought ...

- It is important to recognize that the trajectories of lifetime risk for cardiovascular disease predicted by a PGS are not fixed.
- At the same level of a PGS for CAD, participants with lower lifetime exposure to LDL and SBP had a lower trajectory of risk for cardiovascular disease.
- This finding implies that the trajectory of cardiovascular risk predicted by a PGS can be reduced by lowering LDL and SBP.
- Indeed, participants with low lifetime exposure to LDL and SBP had a low lifetime risk of cardiovascular disease at all levels of PGS for CAD.
- This implies that LDL and SBP, which are modifiable, may be more powerful determinants of lifetime risk than polygenic predisposition.
- Therefore, maintaining low levels of LDL and SBP throughout life should be the primary focus to reduce the lifetime risk of cardiovascular disease for all persons at all levels of PGS for CAD.
Thank you