UHZ

# Application of Non-HDL-Cholesterol for Population-based Cardiovascular Risk Stratification

Stefan Blankenberg on behalf of the
*Multinational Cardiovascular Risk Consortium*

ESC Congress Paris 2019
Together with World Congress of Cardiology

# Declaration of interest

- Others (ASPIRE Cardiovascular grant award, Pfizer)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Abbott Diagnostics, Amgen, Bayer, Siemens Healthcare, Novartis)

# Background

- Causal relationship between blood cholesterol concentration and cardiovascular disease (CVD) is well proven.
- Association between baseline lipid concentrations and very long-term cardiovascular outcomes in the population remains rather sparse.
- Current guideline recommendations for primary prevention are based on the 10-year CVD risk potentially underestimating the cumulative lifetime risk particularly in younger adults.
- In high risk individuals lipid lowering therapy to prevent CVD events is well established. Evidence is less clear for primary prevention in particular in younger individuals.

# Objectives

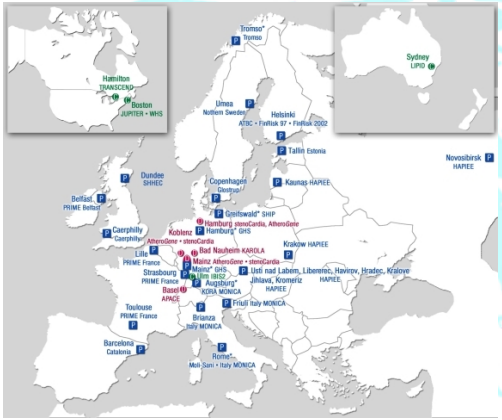
We aim to

- describe the impact of non-HDL-C concentration on long-term risk for CVD
- establish a tool to easily assess the long-term risk probabilities for CVD according to categories of non-HDL-C, age, sex and number of risk factors
- evaluate the potential benefit of an early lipid lowering strategy according to the tools categories

# Multinational Cardiovascular Risk Consortium

## MORGAM/BiomarCaRE

# Multinational Cardiovascular Risk Consortium




| MORGAM/BiomarCaRE |
|---|
| ATBC |
| DanMONICA Study, RCPH |
| EGCUT |
| ESTHER Study |
| FINRISK |
| GHS |
| Kaunas Study |
| KORA MONICA |
| Krakow Study |
| MATISS Rome Study |
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| Novosibirsk Study |
| PRIME |
| SHHEC |
| SHIP |
| Tromsø Study |
| Warsaw Study |

| Further population-based cohorts worldwide |
|---|
| AusDiab |
| Atherosclerosis Risk in Communities Study (ARIC) |
| ATTICA |
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| Cardiovascular Health Study (CHS) |
| Dallas Heart Study (DHS) |
| DETECT |
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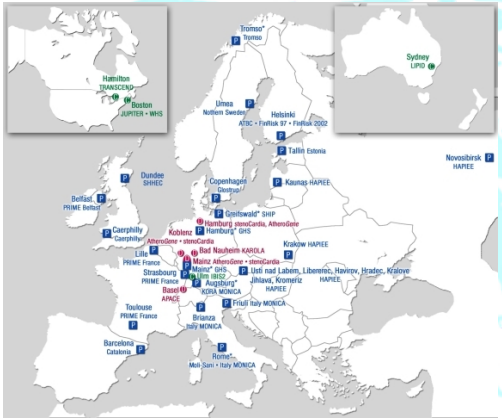
| PREVEND Study |
| ULSAM Study |

# Multinational Cardiovascular Risk Consortium




**36 cohorts**
**19 countries**
**3 continents**

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# Methods

**Study population**

Out of 511,988 individuals of the *Multinational Cardiovascular Risk Consortium* we excluded individuals with prevalent CVD (N=33,234). Information about harmonized incident CVD was available in 380,087 individuals.

Derivation analyses were performed in the MORGAM/BiomarCaRE dataset and results were validated in the non-MORGAM/non-BiomarCaRE cohorts.

**Primary clinical outcome**

non-fatal or fatal CVD defined as the first occurrence of myocardial infarction, unstable angina, coronary death, coronary revascularization, or ischemic stroke.

During max. f/u of 43 years, 47,972 endpoints occurred.

# Methods

**Multivariable analyses**

Analyses were adjusted for potential confounders: age, sex, cohort, and modifiable classical cardiovascular risk factors (smoking status, diabetes, obesity, and arterial hypertension).

**Non-HDL-cholesterol**

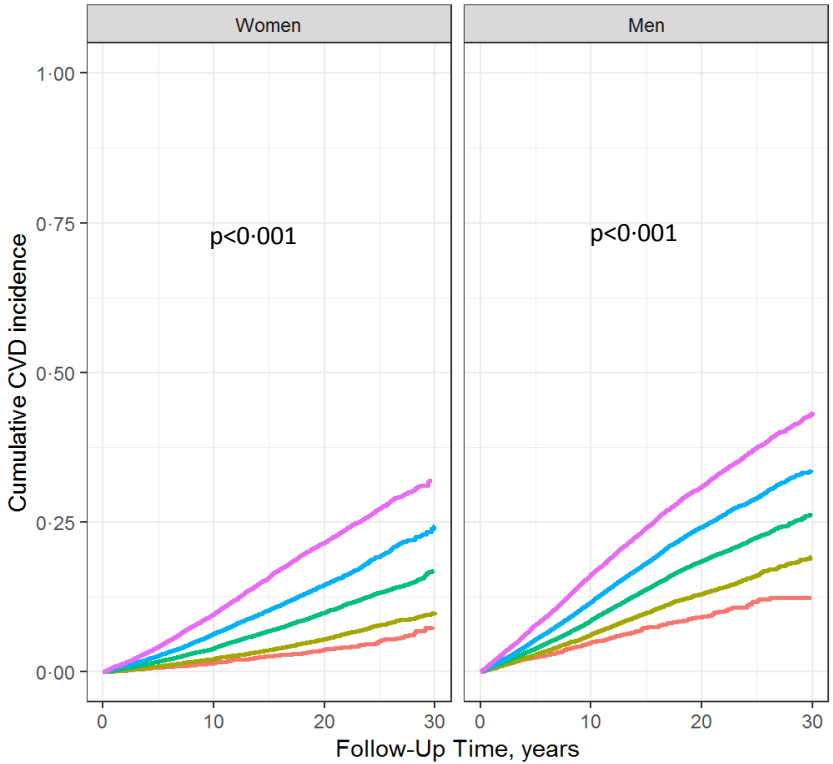
Based on the 2016 ESC/EAS dyslipidaemia guidelines non-HDL-C concentrations were calculated to be 0·8 mmol/L (30 mg/dL) higher compared to LDL-C levels.

Threshold concentrations were displayed in mmol/l assuming 1 mmol/l = 38·67 mg/dL.

# Baseline characteristics

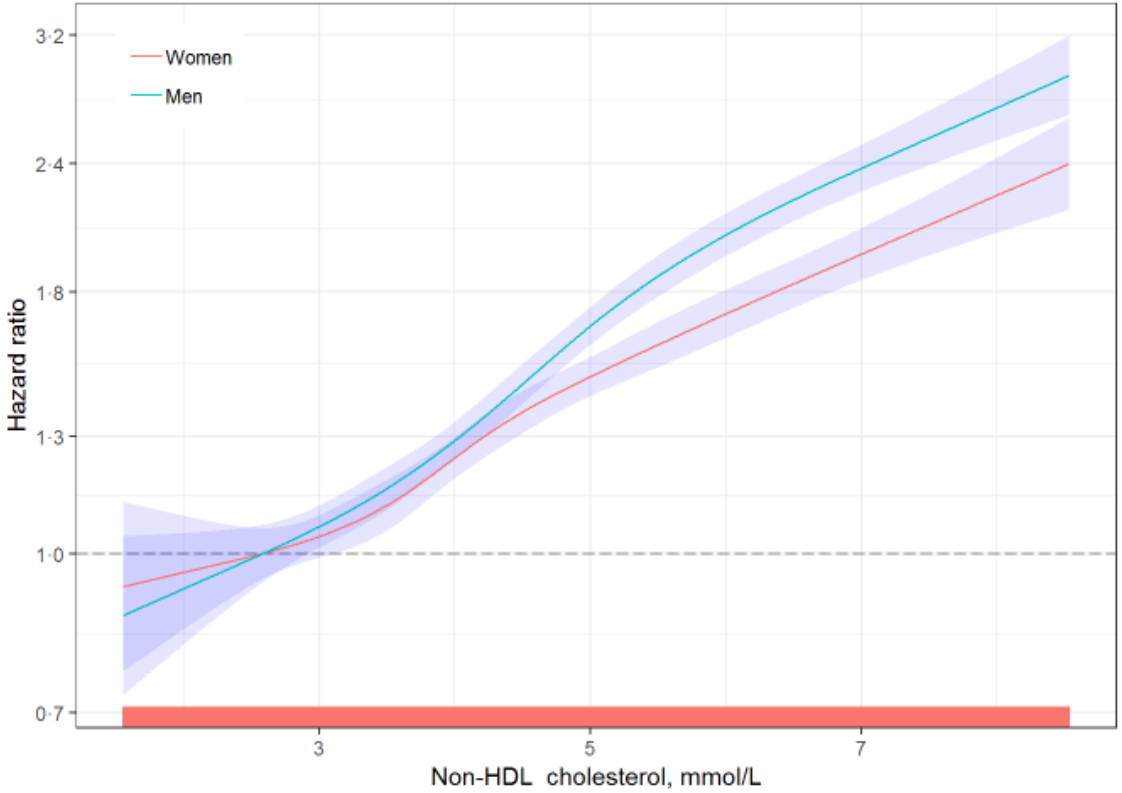
| | All (N= 380,087) | Derivation (N= 226,661) | Validation (N= 153,426) |
|---|---|---|---|
| **Examination years, range** | 1970-2013 | 1982-2013 | 1970-2004 |
| **Examination age (years)** | 50·7 (40·6, 59·2) | 50·4 (38·5, 58·3) | 51·0 (45·0, 61·0) |
| **Follow-up time years, range** | 0-43·6 | 0-30·8 | 0-43·6 |
| **Follow-up years** | 13·2 (6·8, 20·1) | 10·3 (5·6, 16·9) | 20·0 (12·3, 26·5) |
| **Female %** | 48·4 | 47·8 | 49·4 |
| **Risk SCORE** | 1·0 (0·2, 3·4) | 1·2 (0·2, 3·8) | 0·8 (0·2, 2·7) |
| **BMI (kg/m²)** | 25·7 (23·1, 28·8) | 25·8 (23·1, 28·9) | 25·6 (23·1, 28·7) |
| **Arterial hypertension %** | 39·8 | 40·2 | 38·9 |
| **Diabetes mellitus %** | 4·7 | 4·1 | 5·7 |
| **Daily smoker %** | 33·7 | 36·5 | 28·6 |
| **Cholesterol lowering medication %** | 4·6 | 3·7 | 5·9 |
| **LDL-cholesterol (mmol/L)** | 3·6 (2·9, 4·3) | 3·6 (2·9, 4·3) | 3·6 (2·9, 4·3) |
| **Non-HDL-cholesterol (mmol/L)** | 4·3 (3·5, 5·2) | 4·4 (3·6, 5·2) | 4·2 (3·4, 5·0) |

# Long-term incidence of CVD according to non-HDL-C

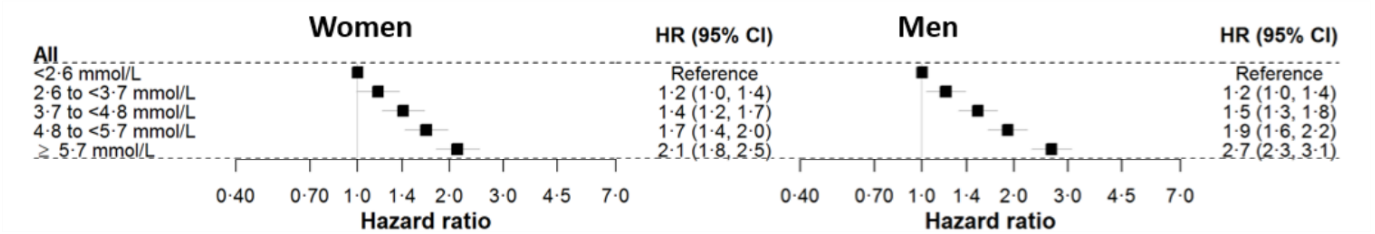



| | |
|---|---|
| <2·6 mmol/L | [< 100 mg/dL] |
| 2·6 to <3·7 mmol/L | [100 to <145 mg/dL] |
| 3·7 to <4·8 mmol/L | [145 to <185 mg/dL] |
| 4·8 to <5·7 mmol/L | [185 to <220 mg/dL] |
| ≥5·7 mmol/L | [≥220 mg/dL] |

# Sex-Specific Linear Association between Long-term incidence of CVD and non-HDL-C



# Age- and sex-specific association of non-HDL-C and CVD



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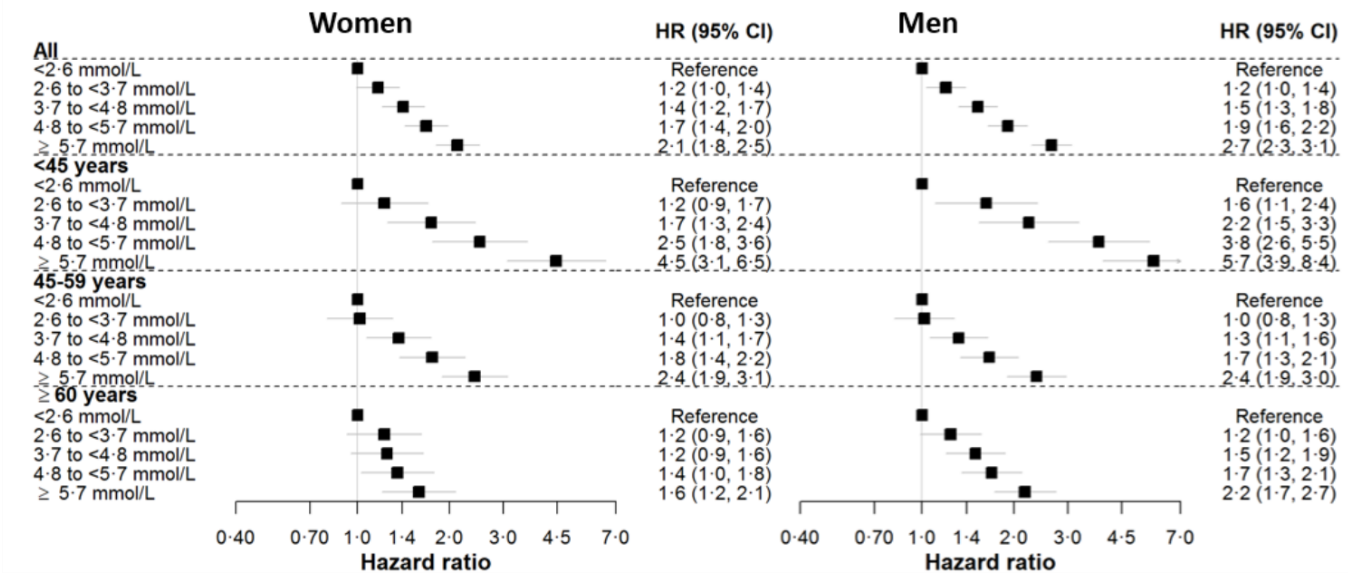
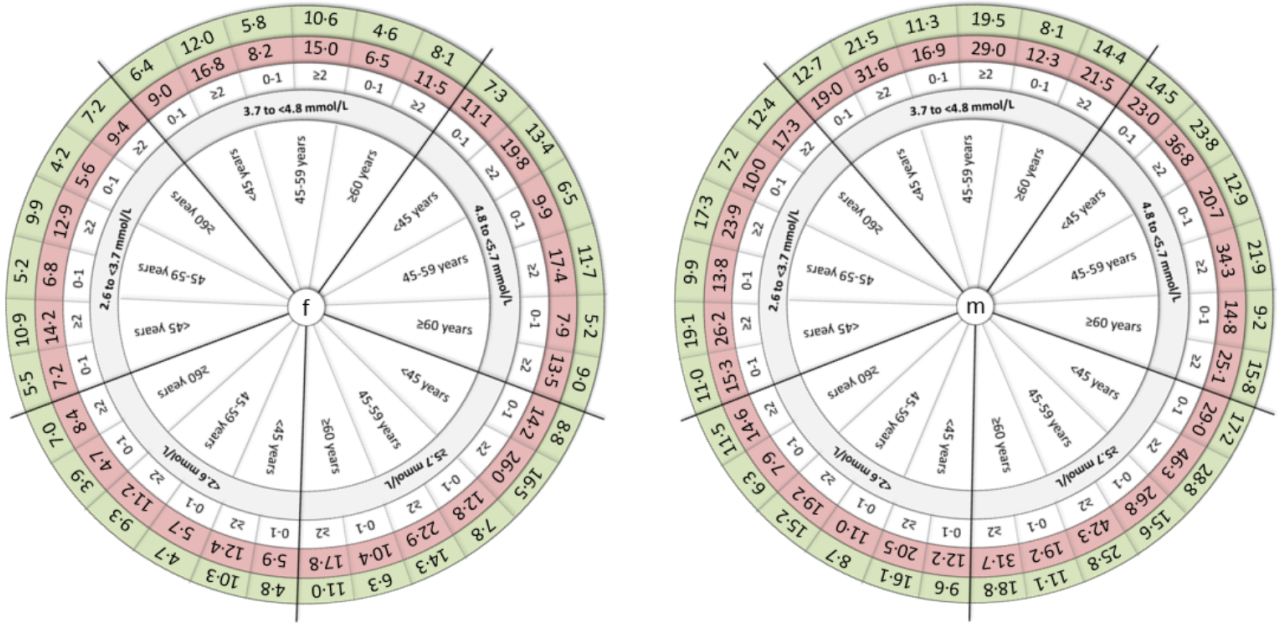
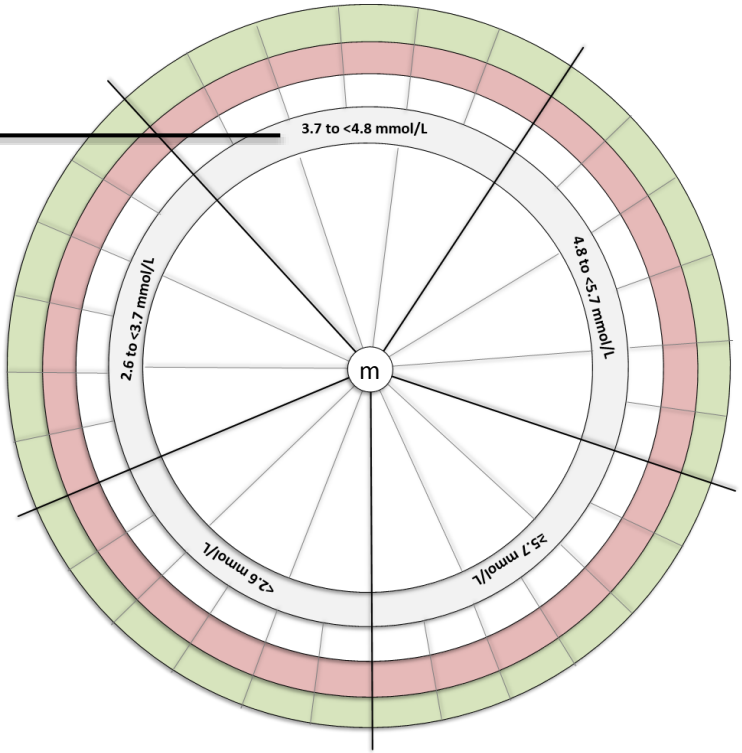


# Model of long-term CVD risk prediction and the simulated benefit of lipid reduction



# Long-term risk model

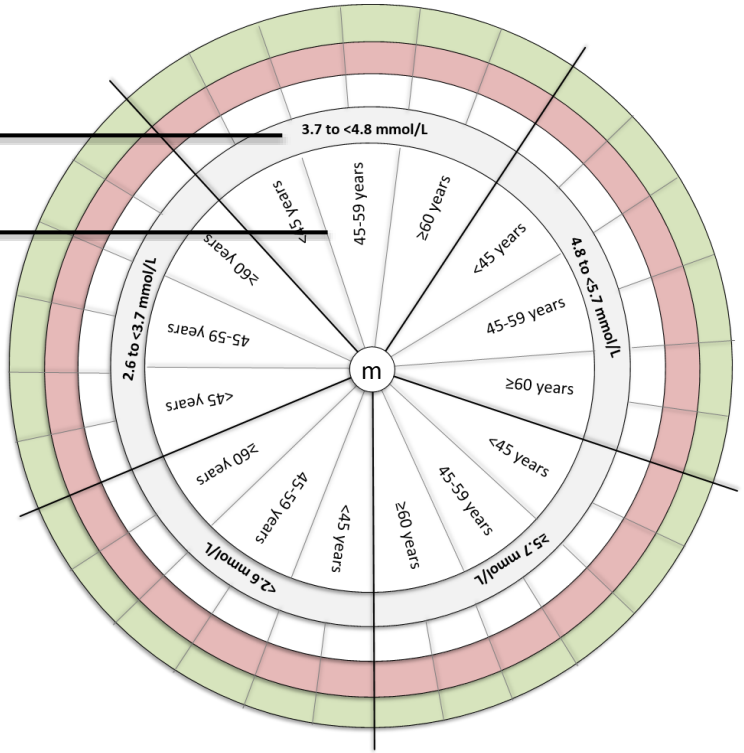
**Five non-HDL-C categories**



# Long-term risk model

**Five non-HDL-C categories**

**Three age-categories within each non-HDL-C category**

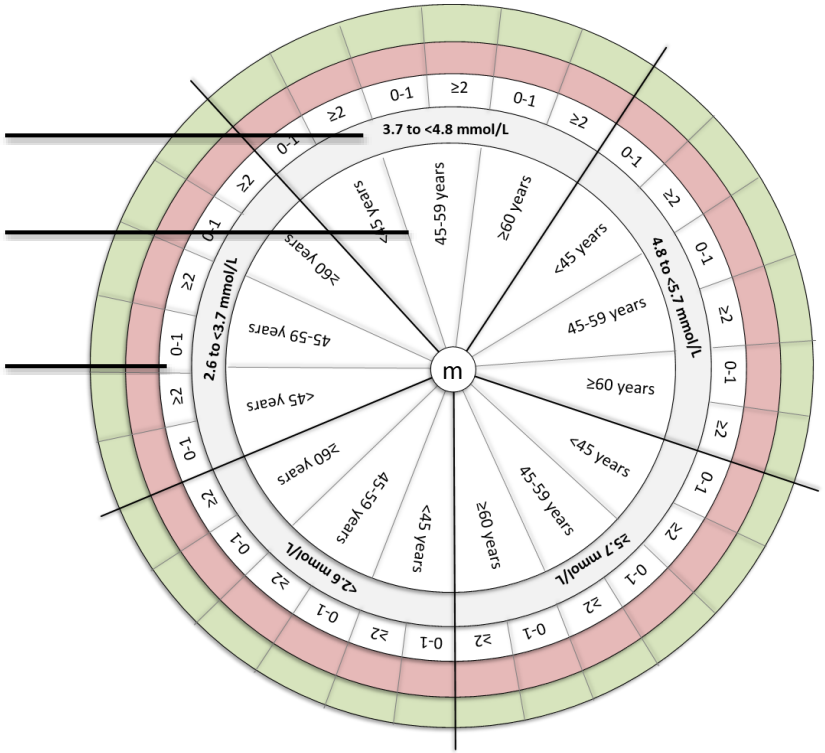


# Long-term risk model

**Five non-HDL-C categories**

**Three age-categories within each non-HDL-C category**

**Number of further CV risk factors (aHT, diabetes, smoking, obesity)**

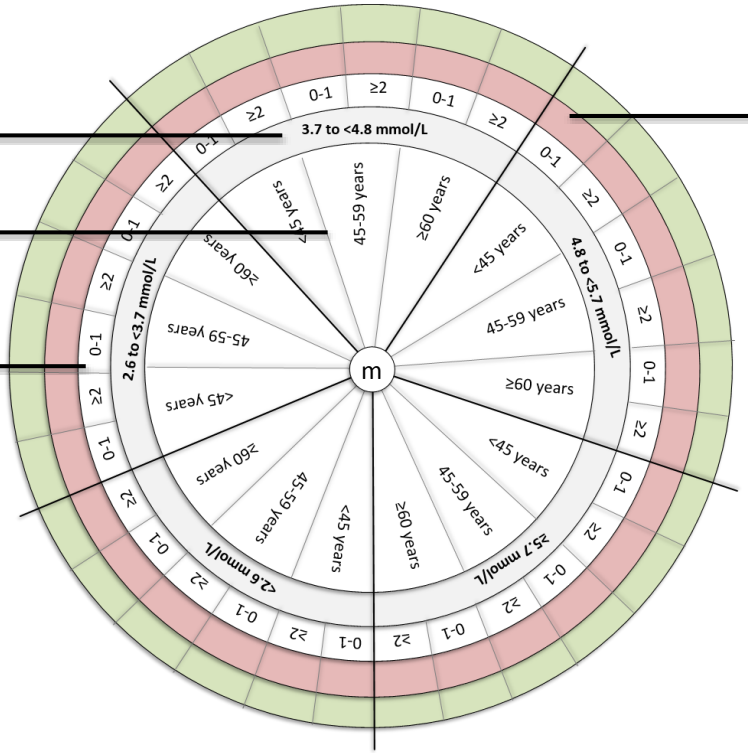


# Long-term risk model

Five non-HDL-C categories

Three age-categories within each non-HDL-C category

Number of further CV risk factors (aHT, diabetes, smoking, obesity)



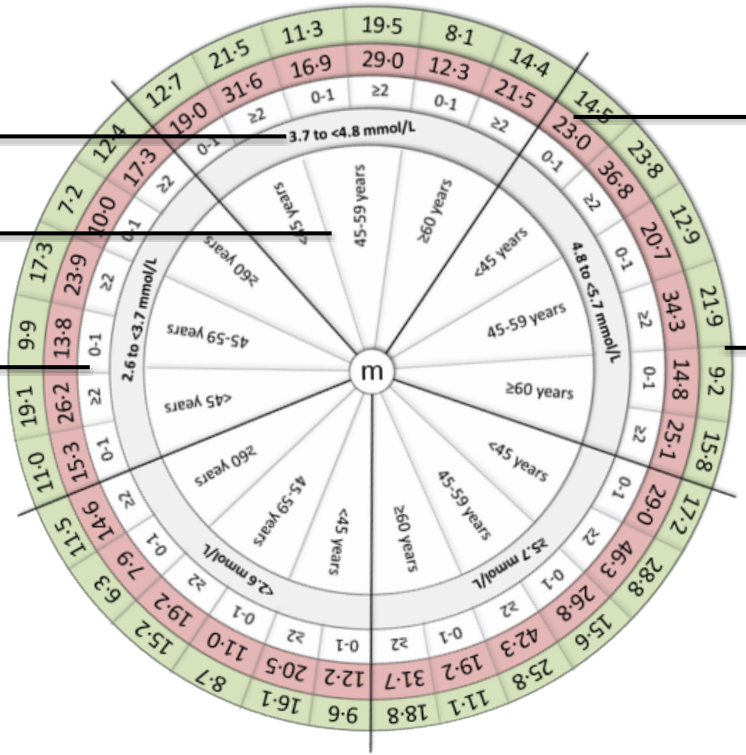

Probability (%) for non-fatal or fatal CVD by the age of 75 years

# Long-term risk model and simulated lifetime lipid reduction

Five non-HDL-C categories

Three age-categories within each non-HDL-C category

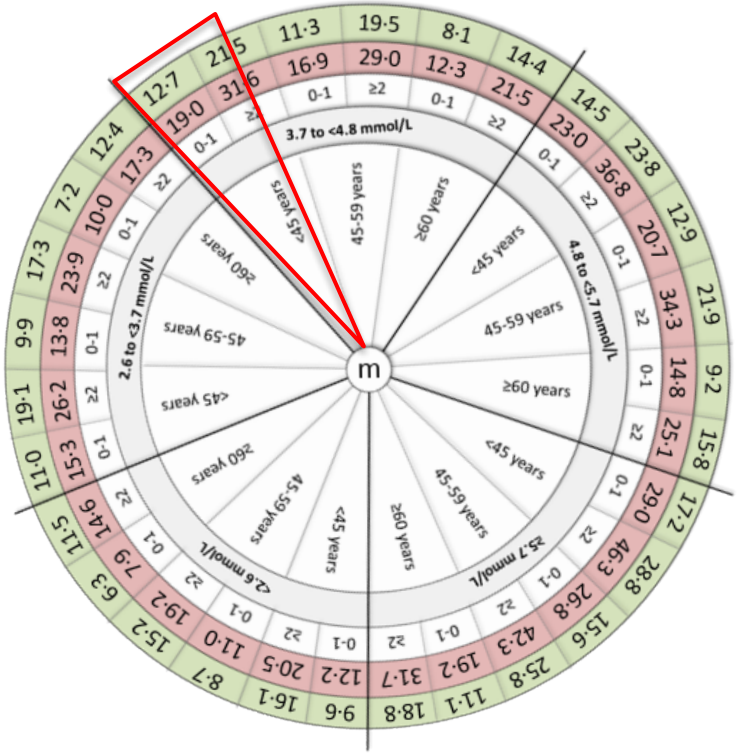
Number of further CV risk factors (aHT, diabetes, smoking, obesity)




Probability (%) for non-fatal or fatal CVD by the age of 75 years

Modelled risk for non-fatal or fatal CVD by the age of 75 years after hypothetical lifetime reduction of non-HDL-C by 50%

# Long-term risk model and simulated lifetime lipid reduction




**Example:** A healthy young man with slightly elevated non-HDL-C of 4·0 mmol/L (155 mg/dL), <45 years of age, and no further CV risk factors. For this individual the non-HDL-based long-term risk for non-fatal or fatal CVD by the age of 75 years is **19·0%** and could be reduced to **12·7%** by 50% lifetime reduction of non-HDL-C blood level (**RRR 33%, NNT 15·9**).

# Limitations

Endpoint information is mainly based on medical reports or local registers. However, endpoint information in all cohorts were harmonized on individual data level according to MORGAM specifications.

The therapeutic benefit of lipid lowering therapy is a hypothetical model assuming lifetime lipid lowering therapy. Therefore, the present study only simulates insights on the benefits of a potential early intervention in primary prevention.

Cohorts were largely based on high income countries (Western Europe, Australia, North America). The generalizability of the findings to other regions, or individuals from other racial/ethnic groups needs to be investigated.

# Conclusion

- We observed a strong graded association of non-HDL-C blood levels and incident CVD during very long-term follow-up with increasing effects over time.

- The risk circles allow the non-HDL-C associated prediction of long-term CVD risk and demonstrate the potential benefit of hypothetical lifetime lipid lowering strategies.

- This simple tool may be practically useful for the physician-patient communication about primary prevention strategies.

# Multinational Cardiovascular Risk Consortium

Fabian J. Brunner, Christoph Waldeyer, Francisco Ojeda, Veikko Salomaa, Frank Kee, Karl Lackner, Philipp Wild, Susana Sans, Annette Peters, Barbara Thorand, Simona Giampaoli, Chiara Donfrancesco, Paolo Brambilla, Stefano G. Signorini, Andres Metspalu, Maris Alver, Hugh Tunstall-Pedoe, Mark Woodward, Satu Männistö, Marie Moitry, Licia Iacoviello, Francesco Gianfagna, Simona Costanzo, Giovanni Veronesi, Guido Grassi, Tom Wilsgaard, Ellisiv B Mathiesen, Stefan Söderberg, Mats Eliasson, Torben Jørgensen, Allan Linneberg, Henry Völzke, Marcus Dörr, Matthias Nauck, Ben Schöttker, Hermann Brenner, Thiess Lorenz, Nataliya Makarova, Raphael Twerenbold, Philippe Amouyel, Jean Dallongeville, Jean Ferrieres, Annette Dobson, Abdonas Tamosiunas, Sofia Malyutina, Yuriy P. Nikitin, Wojciech Drygas, Andrzej Pajak, Olle Melander, Gunnar Engström, Martin Bobak, Karl-Heinz Jöckel, Tuija Jääskeläinen, Teemu Niiranen, Pekka Jousilahti, Graham Giles, Allison Hodge, David M. Leistner, Jens Klotsche, Dianna J. Magliano, Jonathan E. Shaw, Magnus N. Lyngbakken, Kristian Hveem, Demosthenes B. Panagiotakos, Christos Pitsavos, Leon A. Simons, Ramachandran S. Vasan, Emelia J. Benjamin, Robin P.F. Dullaart, Stephan J.L. Bakker, S. Goya Wannamethee, Peter Whincup, Martin Ingelsson, Ulf Risérus, Steven Shea, James A. de Lemos, Torbjørn Omland, Wolfgang Koenig, Tanja Zeller, Jukka Kontto, Kari Kuulasmaa, Ulf Landmesser, and Stefan Blankenberg