Data Article

Data on gender and subgroup specific analyses of omega-3 fatty acids in the Ludwigshafen Risk and Cardiovascular Health Study

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ABSTRACT

This paper contains additional data related to the research article “Omega-3 fatty acids and mortality in patients referred for coronary angiography – The Ludwigshafen Risk and Cardiovascular Health Study” (Kleber et al., in press) [1]. The data shows characteristics of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study according to tertiles of omega-3 fatty acids as well as stratified by gender. The association of proportions of omega-3 fatty acids measured in erythrocyte membranes with different causes of death is investigated with a special focus on modeling the association of EPA with mortality in a nonlinear way. Further, the association of omega-3 fatty acids with all-cause morta-
lity adjusted for high-sensitive C-reactive protein as a marker of systemic inflammation is examined as well as the association of EPA with cause-specific death.

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### Specifications Table

| Subject area                  | Medicine                                               |
|-------------------------------|--------------------------------------------------------|
| More specific subject area    | Cardiovascular diseases                                |
| Type of data                  | Table, graph, figures                                  |
| How data was acquired         | Erythrocyte omega-3 fatty acid proportions were measured at baseline in 3259 participants of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) using the HS-Omega-3 Index method. Associations of omega-3 fatty acid proportions with mortality were investigated using Cox proportional hazards regression. |
| Data format                   | Analyzed                                               |
| Experimental factors          | Fasting blood samples were obtained by venipuncture at study entry. Fatty acid methyl esters were generated from erythrocytes that had been stored at −80 °C by acid transesterification. |
| Experimental features         | Erythrocyte fatty acid composition was analyzed according to the HS-Omega-3 Index technology [2]. Fatty acid methyl esters were analyzed by gas chromatography using a GC2010 gas chromatograph (Shimadzu, Duisburg, Germany) equipped with a 100-m SP2560 column (Supelco, Bellefonte, PA) and using hydrogen as carrier gas. Fatty acids were identified by comparison with a standard mixture of fatty acids characteristic of erythrocytes. Results are presented as a percentage of total identified fatty acids after response factor correction. |
| Data source location          | Ludwigshafen Heart Center in South-West Germany       |
| Data accessibility            | Data is within this article.                           |

### Value of the data

- Gender-stratified analysis allows the identification of gender-specific effects of omega-3 fatty acids.
- Examination of nonlinear effects on mortality risk is important to define safe reference values.
- Investigation of cause-specific mortality might provide hints to possible pathways affected by omega-3 fatty acids.

### 1. Data

The data presented in this paper includes Figures and Tables that show the results of gender and subgroup stratified distribution of omega-3 fatty acids proportions in the LURIC study as well as multivariate adjusted analyses of their association with all-cause and cause-specific mortality that extend the results reported in [1] (Figs. 1–7 and Tables 1–6).
2. Experimental design, materials and methods

2.1. Subjects

The LURIC study consists of 3316 Caucasians with an indication for coronary angiography that were between 1997 and 2000 at the Ludwigshafen Heart Center in South-West Germany. A detailed description of the study can be found in Winkelmann et al. [3]. The study was approved by the 'Landesärztekammer' Ethics Committee of the Rheinland-Pfalz state in Germany. Informed written consent was obtained from all participants.

2.2. Laboratory procedures

The fatty acid composition of erythrocyte membranes was analyzed using the HS-Omega-3 Index® methodology as described in [1,2]. Results are given as a percentage of total identified fatty acids after response factor correction.

Fig. 1. Proportions of omega-3 fatty acids in men and women. Box plots showing the distribution of ALA (A), EPA (B), DHA (C) and DPA (D) in LURIC stratified by gender. Boxes represent the interquartile ranges (IQR), median values are shown as black lines. Whiskers extend to the data point closest to a distance 1.5 times the IQR away from the median. ALA: α-linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid.
2.3. Definition of clinical variables and endpoints

The definition of clinical endpoints is detailed in [1,3]. The 2012 CKD-EPI eGFRcreat-cys equation was used to estimate the glomerular filtration rate [4]. Information on vital status of study participants was requested from local registries. Cardiovascular mortality included sudden cardiac death ($n=254, 7.8\%$), fatal myocardial infarction ($n=104, 3.2\%$), death due to congestive heart failure ($n=148, 4.5\%$), death after intervention to treat CAD ($n=26, 0.8\%$), fatal stroke ($n=60, 1.8\%$), and other causes of death due to CAD ($n=19, 0.6\%$).

2.4. Statistical analyses

We present the mean and the standard deviation of continuous data when normally distributed and the median and 25th and 75th percentile for variables with a skewed distribution. Categorical data are presented as percentages. ANOVA was used to compare continuous variables between groups (variables with a skewed distribution were log-transformed before entering analysis) and the chi-square test was used for categorical variables. The association of omega-3 fatty acid levels in tertiles

![Fig. 2. Density distribution of omega-3 fatty acid levels in men and women. Density plots showing the density distributions of ALA (A), EPA (B), DHA (C) and DPA (D) stratified by gender. ALA: $\alpha$-linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid.](image)
Fig. 3. Association of omega-3 fatty acids with cardiovascular mortality. Forest plot showing the risk of CVM per 1-SD increase in omega-3 fatty acids. Hazard ratios and 95% CI were calculated for ALA, EPA, DHA and the HS-Omega-3 Index by Cox regression. Model 1: adjusted for age and gender; model 2: additionally adjusted for BMI, LDL-C, HDL-C, logTG, hypertension, diabetes, smoking, alcohol consumption, physical exercise and lipid lowering therapy. ALA: α-linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; DPA: docosapentaenoic acid; TG: triglycerides.

Fig. 4. Association of omega-3 fatty acids with mortality additionally adjusted for hsCRP. Forest plot showing the risk of mortality per 1-SD increase in omega-3 fatty acids. Hazard ratios with 95% confidence intervals were calculated by Cox regression adjusted for age and gender, BMI, LDL-C, HDL-C, logTG, hypertension, diabetes, smoking, alcohol consumption, physical exercise, lipid lowering therapy and log hsCRP.

Fig. 5. Association of DPA with mortality. Forest plot showing the risk of all-cause mortality and CVM per 1-SD increase in DPA. Model 1: adjusted for age and gender; model 2: additionally adjusted for BMI, LDL-C, HDL-C, logTG, hypertension, diabetes, smoking, alcohol consumption, physical exercise and lipid lowering therapy. DPA: docosapentaenoic acid.
Fig. 6. Association of omega-3 fatty acids with all-cause mortality stratified by CAD status. Hazard ratios and 95% CI were calculated for ALA, EPA, DHA and the HS-Omega-3 Index using Cox regression in patients with (A) and without (B) CAD at baseline. Model 1: adjusted for age and gender; model 2: additionally adjusted for BMI, LDL-C, HDL-C, logTG, hypertension, diabetes, smoking, alcohol intake, physical exercise and lipid lowering therapy. ALA: α-linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; TG: triglycerides.
or as $Z$-transformed values with mortality was assessed by Cox proportional hazard regression with the same adjustments as in [1]. Examination of scaled Schoenfeld residuals provided no evidence for a violation of the proportional hazard assumption. All tests were two-sided and a $p$ value $< 0.05$ was considered statistically significant. SPSS v22.0 (IBM, Ehningen, Germany) and R v3.2.3 (http://www.r-project.org) were used for all analyses. The R-package 'rms' was used for the generation of hazard ratio plots.

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Table 1
Study characteristics stratified by gender (mean ± SD or median and 25th–75th percentile).

|                | Male       | Female     | p*   |
|----------------|------------|------------|------|
| Age (years)    | 61.8 (64.7)| 64.7 (10.2)| <0.001|
| BMI (kg/m²)    | 27.6 (3.78)| 27.3 (4.66)| 0.103|
| LDL-C (mmol/L) | 2.95 (0.84)| 3.16 (0.98)| <0.001|
| HDL-C (mmol/L) | 0.97 (0.26)| 1.08 (0.31)| <0.001|
| TG (mmol/L)    | 1.67 (1.24–2.28)| 1.63 (1.20–2.26)| 0.016|
| Systolic blood pressure (mmHg) | 141 (23.2) | 141 (24.6) | 0.870|
| Diastolic blood pressure (mmHg) | 81.7 (11.5) | 79.5 (11.4) | <0.001|
| Fasting glucose (mmol/L) | 5.70 (5.23–6.59) | 5.64 (5.14–6.56) | 0.004|
| hsCRP (mg/L)   | 3.28 (1.24–8.63)| 3.58 (1.45–8.63)| 0.107|
| NT-proBNP (ng/ml) | 286 (98.0–858) | 313 (132–878) | 0.002|
| RBC ALA (%)    | 0.118 (0.046)| 0.123 (0.045)| 0.001|
| RBC EPA (%)    | 0.77 (0.32) | 0.75 (0.28) | 0.053|
| RBC DPA (%)    | 2.47 (0.36) | 2.36 (0.336) | <0.001|
| RBC DHA (%)    | 5.05 (1.12) | 5.12 (1.02) | 0.102|
| RBC HS-Omega-3 Index (%) | 5.82 (1.33) | 5.86 (1.19) | 0.365|
| CAD (%)        | 83.6       | 64.7       | <0.001|
| Diabetes mellitus (%) | 40.1       | 39.0       | 0.586|
| Hypertension (%)| 71.4       | 76.2       | 0.005|
| Arrhythmia (%) | 15.4       | 13.1       | 0.930|
| Smoking (active/ex/never) (%) | 26.2/50.7/23.0 | 17.2/19.0/63.8 | <0.001|
| Lipid lowering therapy (%) | 50.6       | 43.9       | <0.001|

* t-test for continuous variables (non-normally distributed variables were log transformed before entering analysis), χ² test for categorical variables.

Table 2
Study characteristics according to tertiles of α-linoleic acid (mean ± SD or median and 25th–75th percentile).

|                   | ≤ 0.10 | 0.11–0.13 | ≥ 0.14 | p*   |
|-------------------|--------|-----------|--------|------|
| N                 | 1384   | 952       | 923    |      |
| Age (years)       | 63.5 ± 10.6 | 62.8 ± 10.8 | 61.5 ± 10.4 | <0.001|
| Sex (% male)      | 72.7   | 69.3      | 65.4   | 0.001|
| BMI (kg/m²)       | 27.6 ± 3.99 | 27.4 ± 4.07 | 27.5 ± 4.18 | 0.455|
| LDL-C (mg/dl)     | 114 ± 32.1 | 117 ± 35.1 | 120 ± 36.4 | <0.001|
| HDL-C (mg/dl)     | 37.4 ± 10.1 | 39.3 ± 11.2 | 40.5 ± 11.4 | <0.001|
| TG (mg/dl)        | 136 (103–185) | 144 (107–197) | 166 (120–236) | <0.001|
| LDL radius (nm)   | 8.28 ± 0.20 | 8.28 ± 0.23 | 8.28 ± 0.24 | 0.815|
| Systolic blood pressure (mmHg) | 141 ± 23.8 | 141 ± 23.4 | 141 ± 23.6 | 0.967|
| Diastolic blood pressure (mmHg) | 80.1 ± 11.6 | 81.2 ± 11.6 | 82.1 ± 11.1 | <0.001|
| Fasting glucose (mg/dl) | 102 (92.7–118) | 103 (94.0–118) | 103 (95.0–119) | 0.104|
| hsCRP (mg/L)      | 4.28 (1.50–10.1) | 3.28 (1.33–8.35) | 2.60 (1.12–6.18) | <0.001|
| NT-proBNP (ng/ml) | 367 (139–1029) | 278 (100–848) | 214 (86.0–604) | <0.001|
| CAD (%)           | 82.5   | 75.4      | 73.5   | <0.001|
| Diabetes (%)      | 40.9   | 39.9      | 37.9   | 0.357|
| Hypertension (%)  | 73.3   | 72.2      | 72.9   | 0.821|
| Arrhythmia (%)    | 15.0   | 16.0      | 12.9   | 0.147|
| Smoking (active/ex/never) (%) | 22.9/44.6/32.5 | 23.0/36.9/40.1 | 24.8/40.1/35.1 | 0.001|
| Lipid lowering therapy (%) | 53.8    | 47.4      | 42.0   | <0.001|

* ANOVA for continuous variables (non-normally distributed variables were log transformed before entering analysis), χ² test for categorical variables.
Table 3
Study characteristics according to tertiles of eicosapentaenoic acid (mean ± SD or median and 25th–75th percentile).

|                  | EPA (% of total fatty acids) |                  |                  |                |                |
|------------------|-----------------------------|------------------|------------------|----------------|----------------|
|                  | ≤ 0.60                      | 0.61–0.62        | ≥ 0.83           |                |                |
| Age (years)      | n = 1096                    | n = 1115         | n = 1048         | p⁺             |                |
|                  | 63.0 ± 10.9                 | 62.3 ± 11.0      | 62.8 ± 9.9       | 0.261          |                |
| Sex (% male)     | 68.8                        | 69.6             | 70.6             | 0.658          |                |
| BMI (kg/m²)      | 27.4 ± 4.0                  | 27.5 ± 4.2       | 27.5 ± 4.0       | 0.830          |                |
| LDL-C (mg/dl)    | 112.1 ± 32.4                | 116.8 ± 35.1     | 120.8 ± 34.8     | < 0.001        |                |
| HDL-C (mg/dl)    | 37.0 (10.1)                 | 38.4 ± 10.2      | 41.1 ± 11.8      | < 0.001        |                |
| TG (mg/dl)       | 153 (113–210)               | 150 (112–206)    | 136 (102–187)    | < 0.001        |                |
| LDL radius (nm)  | 8.27 ± 0.21                 | 8.28 ± 0.23      | 8.30 ± 0.22      | 0.015          |                |
| Systolic blood pressure (mmHg) | 141 ± 23.6          | 140 ± 23.9       | 142 ± 23.4       | 0.295          |                |
| Diastolic blood pressure (mmHg) | 80.7 ± 11.5           | 80.7 ± 11.6      | 81.7 ± 11.3      | 0.076          |                |
| Fasting glucose (mg/dl) | 102 (93.7–120)       | 102 (93.6–119)   | 102 (93.6–116)   | 0.279          |                |
| hsCRP (mg/L)     | 3.74 (1.38–9.30)            | 3.35 (1.35–8.56) | 3.02 (1.18–7.99) | 0.005          |                |
| NT-proBNP (ng/ml)| 352 (136–1118)              | 274 (97.0–773)   | 248 (98.0–756)   | < 0.001        |                |
| CAD (%)          | 78.7                        | 78.5             | 76.3             | 0.341          |                |
| Diabetes (%)     | 43.2                        | 39.1             | 36.8             | 0.009          |                |
| Hypertension (%) | 73.9                        | 72.4             | 72.3             | 0.642          |                |
| Arrhythmia (%)   | 15.5                        | 15               | 13.6             | 0.446          |                |
| Smoking (active/ex/never) (%) | 24.4/41.8/33.9 | 24.2/38.7/37.0 | 21.8/42.7/35.5 | 0.210          |                |
| Lipid lowering therapy (%) | 49.5                     | 49.7             | 46.4             | 0.224          |                |

⁺ ANOVA for continuous variables (non-normally distributed variables were log transformed before entering analysis), χ² test for categorical variables.

Table 4
Study characteristics according to tertiles of docosahexaenoic acid (mean ± SD or median and 25th–75th percentile).

|                  | DHA(% of total fatty acids) |                  |                  |                |                |
|------------------|-----------------------------|------------------|------------------|----------------|----------------|
|                  | ≤ 4.53                      | 4.54–5.47        | ≥ 5.48           |                |                |
| Age (years)      | n = 1090                    | n = 1084         | n = 1085         | p⁺             |                |
|                  | 60.1 ± 11.2                 | 62.6 ± 10.5      | 65.3 ± 9.46      | < 0.001        |                |
| Sex (% male)     | 72.4                        | 69.3             | 67.3             | 0.033          |                |
| BMI (kg/m²)      | 27.2 ± 4.1                  | 27.7 ± 4.0       | 27.4 ± 4.1       | 0.017          |                |
| LDL-C (mg/dl)    | 117.4 ± 33.2                | 117.2 ± 34.6     | 114.8 ± 35.0     | 0.145          |                |
| HDL-C (mg/dl)    | 38.9 ± 10.8                 | 38.4 ± 10.4      | 39.1 ± 11.4      | 0.318          |                |
| TG (mg/dl)       | 156 (112–216)               | 149 (113–203)    | 135 (102–187)    | < 0.001        |                |
| LDL radius (nm)  | 8.27 ± 0.21                 | 8.28 ± 0.23      | 8.29 ± 0.22      | 0.114          |                |
| Systolic blood pressure (mmHg) | 140 ± 23.6          | 141 ± 23.8       | 142 ± 23.4       | 0.237          |                |
| Diastolic blood pressure (mmHg) | 81.3 ± 11.7            | 81.0 ± 11.5      | 80.7 ± 11.2      | 0.391          |                |
| Fasting glucose (mg/dl) | 101 (93.2–115)       | 104 (94.4–120.9) | 102 (93.4–119)   | 0.122          |                |
| hsCRP (mg/L)     | 3.32 (1.24–7.91)            | 3.57 (1.38–9.24) | 3.34 (1.23–8.54) | 0.107          |                |
| NT-proBNP (ng/ml)| 276 (95.8–757)              | 292 (105–934)    | 311 (116–921)    | 0.013          |                |
| CAD (%)          | 75.2                        | 78.5             | 79.9             | 0.026          |                |
| Diabetes (%)     | 35.2                        | 42.3             | 41.8             | 0.001          |                |
| Hypertension (%) | 70.9                        | 74.3             | 73.5             | 0.187          |                |
| Arrhythmia (%)   | 13.5                        | 13.8             | 16.9             | 0.051          |                |
| Smoking (active/ex/never) (%) | 33.0/36.2/30.7 | 23.5/42.4/34.0 | 13.8/44.5/41.7  | < 0.001        |                |
| Lipid lowering therapy (%) | 47.0                     | 48.5             | 50.2             | 0.315          |                |

⁺ ANOVA for continuous variables (non-normally distributed variables were log transformed before entering analysis), χ² test for categorical variables.
Table 5
Comparison of Cox regression analyses modeling EPA proportion as linear term or as restricted cubic spline adjusted for risk factors (model 2).

|                  | loglik     | Chisq     | Df | p       |
|------------------|------------|-----------|----|---------|
| **Combined**     |            |           |    |         |
| Spline model     | – 7151.0   |           |    |         |
| Linear model     | – 7153.5   | 4.9778    | 1  | 0.02567 |
| **Men**          |            |           |    |         |
| Spline model     | – 5072.7   |           |    |         |
| Linear model     | – 5076.3   | 7.1767    | 1  | 0.007386|
| **Women**        |            |           |    |         |
| Spline model     | – 1519.7   |           |    |         |
| Linear model     | – 1519.9   | 0.3817    | 1  | 0.5367  |

Table 6
Association between omega-3 fatty acids and cause-specific death.

|                  | Death due to heart failure | Sudden cardiac death |
|------------------|---------------------------|----------------------|
|                  | HR (95% CI)               | p        | HR (95% CI)     | p        |
| **α-Linolenic acid** |               |           |                |         |
| Model 1          |                           |           |                |         |
| 1st (≤ 0.10%)    | 1 reference              | 1 reference |                   |         |
| 2nd (0.11–0.13%) | 0.75 (0.50–1.12)         | 0.154     | 0.77 (0.57–1.04) | 0.088    |
| 3rd (≥ 0.14%)    | 0.96 (0.65–1.42)         | 0.838     | 0.96 (0.71–1.29) | 0.761    |
| \(P_{\text{Trend}}\) |                           | 0.346     | 0.346           | 0.222    |
| Model 2          |                           |           |                |         |
| 1st (≤ 0.10%)    | 1 reference              | 1 reference |                   |         |
| 2nd (0.11–0.13%) | 0.79 (0.53–1.19)         | 0.258     | 0.80 (0.59–1.09) | 0.159    |
| 3rd (≥ 0.14%)    | 1.05 (0.69–1.58)         | 0.831     | 1.05 (0.77–1.44) | 0.764    |
| \(P_{\text{Trend}}\) |                           | 0.422     | 0.422           | 0.252    |
| **Eicosapentaenoic acid** |               |           |                |         |
| Model 1          |                           |           |                |         |
| 1st (≤ 0.60%)    | 1 reference              | 1 reference |                   |         |
| 2nd (0.61–0.82%) | 0.71 (0.49–1.04)         | 0.077     | 0.93 (0.69–1.24) | 0.600    |
| 3rd (≥ 0.83%)    | 0.62 (0.42–0.93)         | 0.020     | 0.71 (0.52–0.98) | 0.034    |
| \(P_{\text{Trend}}\) |                           | 0.044     | 0.044           | 0.094    |
| Model 2          |                           |           |                |         |
| 1st (≤ 0.60%)    | 1 reference              | 1 reference |                   |         |
| 2nd (0.61–0.82%) | 0.77 (0.52–1.13)         | 0.184     | 0.98 (0.73–1.31) | 0.886    |
| 3rd (≥ 0.83%)    | 0.69 (0.46–1.04)         | 0.076     | 0.75 (0.54–1.04) | 0.081    |
| \(P_{\text{Trend}}\) |                           | 0.167     | 0.167           | 0.165    |
| **Docosahexaenoic acid** |               |           |                |         |
| Model 1          |                           |           |                |         |
| 1st (≤ 4.53%)    | 1 reference              | 1 reference |                   |         |
| 2nd (4.54–5.47%) | 0.80 (0.53–1.20)         | 0.273     | 1.03 (0.76–1.41) | 0.833    |
| 3rd (≥ 5.48%)    | 0.85 (0.57–1.26)         | 0.411     | 0.94 (0.69–1.28) | 0.700    |
| \(P_{\text{Trend}}\) |                           | 0.525     | 0.525           | 0.815    |
| Model 2          |                           |           |                |         |
| 1st (≤ 4.53%)    | 1 reference              | 1 reference |                   |         |
| 2nd (4.54–5.47%) | 0.76 (0.50–1.15)         | 0.197     | 0.95 (0.69–1.30) | 0.741    |
| 3rd (≥ 5.48%)    | 0.84 (0.56–1.26)         | 0.388     | 0.91 (0.66–1.26) | 0.574    |
| \(P_{\text{Trend}}\) |                           | 0.425     | 0.425           | 0.853    |
| **HS-Omega-3 Index** |               |           |                |         |
| Model 1          |                           |           |                |         |
| 1st (≤ 5.19%)    | 1 reference              | 1 reference |                   |         |
| 2nd (5.20–6.24%) | 0.74 (0.49–1.10)         | 0.137     | 1.11 (0.82–1.50) | 0.517    |
| 3rd (≥ 6.25%)    | 0.77 (0.52–1.13)         | 0.182     | 0.85 (0.62–1.16) | 0.305    |
| \(P_{\text{Trend}}\) |                           | 0.260     | 0.260           | 0.212    |
| Model 2          |                           |           |                |         |
| 1st (≤ 5.19%)    | 1 reference              | 1 reference |                   |         |
| 2nd (5.20–6.24%) | 0.73 (0.49–1.10)         | 0.133     | 1.04 (0.76–1.41) | 0.822    |
| 3rd (≥ 6.25%)    | 0.78 (0.52–1.16)         | 0.221     | 0.82 (0.60–1.14) | 0.242    |
| \(P_{\text{Trend}}\) |                           | 0.278     | 0.278           | 0.303    |

Model 1: adjusted for age and gender.
Model 2: additionally adjusted for LDL-C, HDL-C, logTG, BMI, hypertension, diabetes mellitus, smoking, alcohol intake, physical exercise and lipid lowering therapy.
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Transparency document. Supplementary material

Transparency data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.dib.2016.07.051.

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