

# Heme oxygenase 1 polymorphism, occupational vapor, gas, dust, and fume exposure and chronic obstructive pulmonary disease in a Danish population-based study<sup>1</sup>

by Else Toft Würtz, PhD,<sup>2</sup> Charlotte Brasch-Andersen, PhD, Rudi Steffensen, PhD, Jens Georg Hansen, DMSc, Tine Halsen Malling, PhD, Vivi Schlünssen, PhD, Øyvind Omrand, PhD

1. *Supplementary tables*

2. *Correspondence to: Else Toft Würtz, Department of Occupational and Environmental Medicine, Danish Ramazzini Centre, Aalborg University Hospital, Havrevangen 1,4, 9000 Aalborg, Denmark. [E-mail: etw@rn.dk]*

**Supplementary Table S1.** A priori specialist identified jobs with known occupational exposures to vapour, gas, dust, or fumes, selected 72 out of 372 DISCO-88 codes.

| Job description <sup>a</sup>                                                  | Unit group <sup>a</sup> |               |          |
|-------------------------------------------------------------------------------|-------------------------|---------------|----------|
|                                                                               | ISCO-88                 | ISCO-88 (COM) | DISCO-88 |
| General managers in agriculture, hunting, forestry and fishing                | 1311                    | 1311          | 1311     |
| General managers in manufacturing                                             | 1312                    | 1312          | 1312     |
| General managers in construction                                              | 1313                    | 1313          | 1313     |
| General managers in personal care, cleaning and related services              | 1318                    | 1318          | 1318     |
| Agronomists and related professionals                                         | 2213                    | 2213          | 2213     |
| Veterinarians                                                                 | 2223                    | 2223          | 2223     |
| Veterinary assistants                                                         | 3227                    | 3227          | 3227     |
| Fire-fighters                                                                 | 5161                    | 5161          | 5161     |
| Field crop and vegetable growers                                              | 6111                    | 6111          | 6111     |
| Dairy and livestock producers                                                 | 6121                    | 6121          | 6121     |
| Poultry producers                                                             | 6122                    | 6122          | 6122     |
| Market-oriented animal producers and related workers not elsewhere classified | 6129                    | 6129          | 6129     |
| Market-oriented crop and animal producers                                     | 6130                    | 6130          | 6130     |
| Forestry workers and loggers                                                  | 6141                    | 6141          | 6141     |
| Miners and quarry workers                                                     | 7111                    | 7111          | 7111     |
| Stone splitters, cutters and carvers                                          | 7113                    | 7113          | 7113     |
| Builders, traditional materials                                               | 7121                    | 7121          | 7121     |
| Bricklayers and stonemasons                                                   | 7122                    | 7122          | 7122     |
| Concrete placers, concrete finishers and related workers                      | 7123                    | 7123          | 7123     |
| Carpenters and joiners                                                        | 7124                    | 7124          | 7124     |
| Roofers                                                                       | 7131                    | 7131          | 7131     |
| Floor layers and tile setters                                                 | 7132                    | 7132          | 7132     |
| Plasterers                                                                    | 7133                    | 7133          | 7133     |
| Insulation workers                                                            | 7134                    | 7134          | 7134     |
| Painters and related workers                                                  | 7141                    | 7141          | 7141     |
| Varnishers and related painters                                               | 7142                    | -             | 7142     |
| Building structure cleaners                                                   | 7143                    | 7143          | 7143     |
| Metal moulders and coremakers                                                 | 7211                    | 7211          | 7211     |
| Welders and flamecutters                                                      | 7212                    | 7212          | 7212     |
| Sheet-metal workers                                                           | 7213                    | 7213          | 7213     |
| Structural-metal preparers and erectors                                       | 7214                    | 7214          | 7214     |
| Riggers and cable splicers                                                    | 7215                    | 7215          | 7215     |

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**Supplementary Table S1: Continued**

| <b>Job description<sup>a</sup></b>                                            | <b>Unit group<sup>a</sup></b> |                      |                 |
|-------------------------------------------------------------------------------|-------------------------------|----------------------|-----------------|
|                                                                               | <b>ISCO-88</b>                | <b>ISCO-88 (COM)</b> | <b>DISCO-88</b> |
| Metal wheel-grinders, polishers and tool sharpeners                           | 7224                          | 7224                 | 7224            |
| Butchers, fishmongers and related food preparers                              | 7411                          | 7411                 | 7411            |
| Bakers, pastry-cooks and confectionery makers                                 | 7412                          | 7412                 | 7412            |
| Tobacco preparers and tobacco products makers                                 | 7416                          | 7416                 | 7416            |
| Wood treaters                                                                 | 7421                          | 7421                 | 7421            |
| Woodworking-machine setters and setter-operators                              | 7423                          | 7423                 | 7423            |
| Mining-plant operators                                                        | 8111                          | 8111                 | 8111            |
| Mineral-ore- and stone-processing-plant operators                             | 8112                          | 8112                 | 8112            |
| Well drillers and borers and related workers                                  | 8113                          | 8113                 | 8113            |
| Ore and metal furnace operators                                               | 8121                          | 8121                 | 8121            |
| Metal melters, casters and rolling-mill operators                             | 8122                          | 8122                 | 8122            |
| Metal-heat-treating-plant operators                                           | 8123                          | 8123                 | 8123            |
| Glass and ceramics kiln and related machine operators                         | 8131                          | 8131                 | 8131            |
| Wood-processing-plant operators                                               | 8141                          | 8141                 | 8141            |
| Papermaking-plant operators                                                   | 8143                          | 8143                 | 8143            |
| Crushing-, grinding- and chemical-mixing-machinery operators                  | 8151                          | 8151                 | 8151            |
| Chemical-heat-treating-plant operators                                        | 8152                          | 8152                 | 8152            |
| Cement and other mineral products machine operators                           | 8212                          | 8212                 | 8212            |
| Ammunition- and explosive-products machine operators                          | 8222                          | 8222                 | 8222            |
| Metal finishing-, plating- and coating-machine operators                      | 8223                          | 8223                 | 8223            |
| Wood-products machine operators                                               | 8240                          | 8240                 | 8240            |
| Bookbinding-machine operators                                                 | 8252                          | 8252                 | 8252            |
| Paper-products machine operators                                              | 8253                          | 8253                 | 8253            |
| Fibre-preparing-, spinning- and winding-machine operators                     | 8261                          | 8261                 | 8261            |
| Grain- and spice-milling-machine operators                                    | 8273                          | 8273                 | 8273            |
| Baked-goods, cereal and chocolate-products machine operators                  | 8274                          | 8274                 | 8274            |
| Sugar production machine operators                                            | 8276                          | 8276                 | 8276            |
| Tea-, coffee-, and cocoa-processing-machine operators                         | 8277                          | 8277                 | 8277            |
| Tobacco production machine operators                                          | 8279                          | 8279                 | 8279            |
| Wood and related products assemblers                                          | 8285                          | 8285                 | 8285            |
| Motorised farm and forestry plant operators                                   | 8331                          | 8331                 | 8331            |
| Earth-moving- and related plant operators                                     | 8332                          | 8332                 | 8332            |
| Garbage collectors                                                            | 9161                          | 9161                 | 9161            |
| Sweepers and related labourers                                                | 9162                          | 9162                 | 9162            |
| Farm-hands and labourers                                                      | 9211                          | 9211                 | 9211            |
| Forestry labourers                                                            | 9212                          | 9212                 | 9212            |
| Mining and quarrying labourers                                                | 9311                          | 9311                 | 9311            |
| Construction and maintenance labourers: roads, dams and similar constructions | 9312                          | 9312                 | 9312            |
| Building construction labourers                                               | 9313                          | 9313                 | 9313            |
| Transport labourers and freight handlers                                      | -                             | 9330                 | 9330            |

ISCO-88: The International Standard Classification of Occupations, revision 1988

ISCO-88 (COM): The International Standard Classification of Occupations, revision 1988 for the European Union (Eurostat)

DISCO-88: Danish adaptation of The International Standard Classification of Occupations, revision 1988

<sup>a</sup> Statistics Denmark (3 April, 2014): <http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx>

**Supplementary Table S2.**

A: Interaction between *HMOX1* L± genotype and VGDF exposure on the risk of COPD, without any adjustments, n=3,871.

|                                     | <i>HMOX1</i> genotype according to L±      |      |           |         |                                                     |             |                  |         | <i>HMOX1</i> ORs within VGDF strata |                  |         |
|-------------------------------------|--------------------------------------------|------|-----------|---------|-----------------------------------------------------|-------------|------------------|---------|-------------------------------------|------------------|---------|
|                                     | No long <i>HMOX1</i> promoter alleles (L-) |      |           |         | At least one long <i>HMOX1</i> promoter allele (L+) |             |                  |         |                                     |                  |         |
|                                     | n COPD/non-COPD                            | OR   | 95% CI    | p-value | n COPD/non-COPD                                     | OR          | 95% CI           | p-value | OR                                  | 95% CI           | p-value |
| VGDF - Never                        | 87/1,722                                   | 1.00 |           |         | 11/209                                              | 1.04        | 0.55-1.98        | 0.90    | 1.04                                | 0.55-1.98        | 0.90    |
| - Ever                              | 104/1,556                                  | 1.32 | 0.99-1.77 | 0.06    | 23/159                                              | <b>2.86</b> | <b>1.76-4.66</b> | <0.01   | <b>2.16</b>                         | <b>1.34-3.50</b> | <0.01   |
| VGDF ORs within <i>HMOX1</i> strata |                                            | 1.32 | 0.99-1.77 | 0.06    |                                                     | <b>2.75</b> | <b>1.30-5.80</b> | 0.01    |                                     |                  |         |

Measure of interaction on additive scale: RERI<sub>OR</sub> (95% CI) = **1.50 (0.07-2.93)**; p=0.04. Measure of interaction on multiplicative scale: ratio of ORs (95% CI) = 2.08 (0.93-4.64); p=0.07.

B: Interaction between *HMOX1* L± genotype and VGDF exposure on the risk of COPD, adjusted for sex, age and general practitioner practice, n=3,871.

|                                     | <i>HMOX1</i> genotype according to L±      |      |           |         |                                                     |             |                  |         | <i>HMOX1</i> ORs within VGDF strata |                  |         |
|-------------------------------------|--------------------------------------------|------|-----------|---------|-----------------------------------------------------|-------------|------------------|---------|-------------------------------------|------------------|---------|
|                                     | No long <i>HMOX1</i> promoter alleles (L-) |      |           |         | At least one long <i>HMOX1</i> promoter allele (L+) |             |                  |         |                                     |                  |         |
|                                     | n COPD/non-COPD                            | OR   | 95% CI    | p-value | n COPD/non-COPD                                     | OR          | 95% CI           | p-value | OR                                  | 95% CI           | p-value |
| VGDF - Never                        | 87/1,722                                   | 1.00 |           |         | 11/209                                              | 1.04        | 0.55-1.99        | 0.90    | 1.04                                | 0.54-2.00        | 0.90    |
| - Ever                              | 104/1,556                                  | 1.16 | 0.84-1.59 | 0.38    | 23/159                                              | <b>2.67</b> | <b>1.61-4.43</b> | <0.01   | <b>2.33</b>                         | <b>1.43-3.81</b> | <0.01   |
| VGDF ORs within <i>HMOX1</i> strata |                                            | 1.16 | 0.84-1.61 | 0.36    |                                                     | <b>2.62</b> | <b>1.15-5.95</b> | 0.02    |                                     |                  |         |

Measure of interaction on additive scale: RERI<sub>OR</sub> (95% CI) = **1.47 (0.09-2.84)**; p=0.04. Measure of interaction on multiplicative scale: ratio of ORs (95% CI) = 2.21 (0.98-4.98); p=0.05.

VGDF: Vapour, gas, dust, or fume occupational exposure. *HMOX1*: Heme oxygenase 1 gene. L-: no-polymorphism, less than 33 (GT) promoter repeats. L+: (GT)<sub>n</sub> promoter repeat polymorphism, including 33 (GT) repeats or more. RERI: relative excess risk due to interaction. Bold estimates: Statistically significant, p<0.05.

### Supplementary Table S3.

Associations between chronic obstructive pulmonary disease and *HMOX1* polymorphism with interaction between *HMOX1* and occupational VGDF exposure with and without smoking interaction in the NCPS study, n<sup>a</sup>=3,871.

|                                                    | Adjusted OR <sup>b</sup> |                   | Adjusted OR <sup>b</sup><br>+ smoking interaction |                   |
|----------------------------------------------------|--------------------------|-------------------|---------------------------------------------------|-------------------|
|                                                    | OR                       | 95% CI            | OR                                                | 95% CI            |
| <i>HMOX1</i> - L-                                  | 1                        |                   | 1                                                 |                   |
| - L+                                               | 1.06                     | 0.55-2.06         | 0.97                                              | 0.33-2.91         |
| Pack-years of smoking                              |                          |                   |                                                   |                   |
| <10                                                | 1                        |                   | 1                                                 |                   |
| 10-20                                              | <b>2.70</b>              | <b>1.58-4.61</b>  | <b>2.68</b>                                       | <b>1.50-4.81</b>  |
| >20                                                | <b>7.67</b>              | <b>5.15-11.42</b> | <b>7.52</b>                                       | <b>4.90-11.54</b> |
| Pack-years of smoking and <i>HMOX1</i> interaction |                          |                   |                                                   |                   |
| <10/L-                                             | -                        |                   | 1                                                 |                   |
| 10-20/L+                                           | -                        | -                 | 1.03                                              | 0.23-4.57         |
| >20/L+                                             | -                        | -                 | 1.13                                              | 0.38-3.35         |
| Sex - Female                                       | 1                        |                   | 1                                                 |                   |
| - Male                                             | <b>0.55</b>              | <b>0.38-0.79</b>  | <b>0.55</b>                                       | <b>0.38-0.79</b>  |
| Age, study population "NCPS"                       |                          |                   |                                                   |                   |
| 45-54                                              | 1                        |                   | 1                                                 |                   |
| 55-64                                              | 1.32                     | 0.78-2.23         | 1.32                                              | 0.78-2.24         |
| 65-74                                              | <b>2.29</b>              | <b>1.43-3.66</b>  | <b>2.29</b>                                       | <b>1.44-3.67</b>  |
| 75-84                                              | <b>2.38</b>              | <b>1.42-3.99</b>  | <b>2.38</b>                                       | <b>1.42-4.00</b>  |
| VGDF - Never                                       | 1                        |                   | 1                                                 |                   |
| - Ever                                             | 1.21                     | 0.87-1.69         | 1.22                                              | 0.87-1.69         |
| VGDF and <i>HMOX1</i> interaction                  |                          |                   |                                                   |                   |
| Never/L-                                           | 1                        |                   | 1                                                 |                   |
| Ever/L+                                            | <b>2.38</b>              | <b>1.04-5.46</b>  | <b>2.36</b>                                       | <b>1.03-5.45</b>  |

<sup>a</sup>Only sex and age were measured among all participants. <sup>b</sup>Adjusted for pack-years of smoking, sex, age, VGDF and additional non-reported adjustments including general practitioner practice in a mixed random effect logistic regression. VGDF: Vapour, gas, dust, or fume occupational exposure. *HMOX1*: Heme oxygenase 1 gene. L-: no-polymorphism, less than 33 (GT) promoter repeats. L+: (GT)<sub>n</sub> promoter repeat polymorphism, including 33 (GT) repeats or more. -: Not included in the model. Bold estimates: Statistically significant, p<0.05.

**Supplementary Table S4.**

Associations between chronic obstructive pulmonary disease and *HMOX1* polymorphism with the VGDF/*HMOX1* interaction with different dichotomisation levels of VGDF exposure.

| VGDF level                        | Adjusted OR <sup>a</sup> with interaction between <i>HMOX1</i> and VGDF |                   |                               |                   |                               |                   |
|-----------------------------------|-------------------------------------------------------------------------|-------------------|-------------------------------|-------------------|-------------------------------|-------------------|
|                                   | As in Table 2: Never vs low/medium/high                                 |                   | New: Never/low vs medium/high |                   | New: Never/low/medium vs high |                   |
|                                   | OR                                                                      | 95% CI            | OR                            | 95% CI            | OR                            | 95% CI            |
| n <sup>b</sup>                    | 3,871                                                                   |                   | 3,871                         |                   | 3,871                         |                   |
| <i>HMOX1</i> - L-                 | 1                                                                       |                   | 1                             |                   | 1                             |                   |
| - L+                              | 1.06                                                                    | 0.55-2.06         | 1.00                          | 0.60-2.02         | 1.52                          | 0.92-2.49         |
| Pack-years of smoking             |                                                                         |                   |                               |                   |                               |                   |
| <10                               | 1                                                                       |                   | 1                             |                   | 1                             |                   |
| 10-20                             | <b>2.70</b>                                                             | <b>1.58-4.61</b>  | <b>2.70</b>                   | <b>1.58-4.62</b>  | <b>2.67</b>                   | <b>1.56-4.56</b>  |
| >20                               | <b>7.67</b>                                                             | <b>5.15-11.42</b> | <b>7.70</b>                   | <b>5.17-11.47</b> | <b>7.64</b>                   | <b>5.13-11.38</b> |
| Sex - Female                      | 1                                                                       |                   | 1                             |                   | 1                             |                   |
| - Male                            | <b>0.55</b>                                                             | <b>0.38-0.79</b>  | <b>0.55</b>                   | <b>0.38-0.80</b>  | <b>0.59</b>                   | <b>0.41-0.85</b>  |
| Age, study population "NCPS"      |                                                                         |                   |                               |                   |                               |                   |
| 45-54                             | 1                                                                       |                   | 1                             |                   | 1                             |                   |
| 55-64                             | 1.32                                                                    | 0.78-2.23         | 1.32                          | 0.78-2.22         | 1.30                          | 0.77-2.20         |
| 65-74                             | <b>2.29</b>                                                             | <b>1.43-3.66</b>  | <b>2.25</b>                   | <b>1.41-3.60</b>  | <b>2.23</b>                   | <b>1.39-3.57</b>  |
| 75-84                             | <b>2.38</b>                                                             | <b>1.42-3.99</b>  | <b>2.32</b>                   | <b>1.38-3.90</b>  | <b>2.29</b>                   | <b>1.36-3.86</b>  |
| VGDF - Never                      | 1                                                                       |                   | 1                             |                   | 1                             |                   |
| - Ever                            | 1.21                                                                    | 0.87-1.69         | 1.23                          | 0.88-1.70         | 1.16                          | 0.83-1.62         |
| VGDF and <i>HMOX1</i> interaction |                                                                         |                   |                               |                   |                               |                   |
| Never/L-                          | 1                                                                       |                   | 1                             |                   | 1                             |                   |
| Ever/L+                           | <b>2.38</b>                                                             | <b>1.04-5.46</b>  | <b>2.50</b>                   | <b>1.11-5.63</b>  | 1.50                          | 0.66-3.45         |

<sup>a</sup>Adjusted for pack-years of smoking, sex, age, VGDF and additional non-reported adjustments including general practitioner practice in a mixed random effect logistic regression. <sup>b</sup>Only sex and age were measured among all participants. VGDF: Vapour, gas, dust, or fume occupational exposure. *HMOX1*: Heme oxygenase 1 gene. L-: no-polymorphism, less than 33 (GT) promoter repeats. L+: (GT)<sub>n</sub> promoter repeat polymorphism, including 33 (GT) repeats or more. Bold estimates: Statistically significant, p<0.05.