**SUPPLEMENTARY MATERIAL**

**Risk factors for incident heart failure with preserved or reduced ejection fraction, and valvular heart failure, in a community-based cohort**

Fei Fei Gong1,2,3, Michael V. Jelinek2,3, Julian M. Castro3, Jennifer M. Coller3, Michele McGrady4, Umberto Boffa4, Louise Shiel4, Danny Liew4, Rory Wolfe4, Simon Stewart,5 Alice J. Owen4, Henry Krum4†, Christopher M. Reid4,6, David L. Prior2,3, and Duncan J. Campbell1,2,3\*

1St. Vincent's Institute of Medical Research, 2University of Melbourne, 3St. Vincent's Hospital, Melbourne, 4School of Public Health and Preventive Medicine, Monash University, 5Mary MacKillop Institute for Health Research, Australian Catholic University, 6School of Public Health, Curtin University, Australia

†Deceased

Corresponding author:

Duncan J. Campbell, St. Vincent's Institute of Medical Research, 41 Victoria Parade, Fitzroy, Victoria 3065, Australia. Tel: 03 9288 2501. Fax: 03 9416 2676. Email: dcampbell@svi.edu.au

**Supplementary Table 1.** Cox regression: univariate subdistribution hazard ratios

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Total HF  HR (95% CI) | *P*-value | HFpEF  HR (95% CI) | *P*-value | HFrEF  HR (95% CI) | *P*-value | VHF  HR (95% CI) | *P*-value |
| Age (per decade) | 2.5 (2.1, 3.1) | <0.0001 | 2.9 (2.1, 3.8) | <0.0001 | 2.5 (1.7, 3.6) | <0.0001 | 1.9 (1.2, 3.1) | 0.011 |
| Male gender | 1.3 (0.9, 1.8) | 0.13 | 0.7 (0.4, 1.1) | 0.1 | 3.6 (1.8, 7.1) | 0.0003 | 1.3 (0.7, 2.5) | 0.46 |
| SBP (per 10 mmHg) | 1.1 (1.0, 1.2) | 0.047 | 1.1 (1.0, 1.3) | 0.13 | 1.1 (1.0, 1.3) | 0.12 | 1.0 (0.8, 1.2) | 0.95 |
| DBP (per 10 mmHg) | 0.84 (0.7, 1.0) | 0.055 | 0.9 (0.7, 1.2) | 0.49 | 0.9 (0.7, 1.3) | 0.65 | 0.6 (0.5, 0.9) | 0.0054 |
| PP (per 10 mmHg) | 1.21 (1.10, 1.34) | <0.0001 | 1.19 (1.03, 1.38) | 0.017 | 1.22 (1.04, 1.43) | 0.012 | 1.22 (1.00, 1.50) | 0.056 |
| log Heart rate (per doubling) | 0.4 (0.2, 0.9) | 0.018 | 0.4 (0.2, 1.1) | 0.066 | 0.6 (0.2, 2.2) | 0.41 | 0.4 (0.1, 1.4) | 0.14 |
| log BMI (per doubling) | 3.8 (2.0, 7.1) | <0.0001 | 15 (6, 35) | <0.0001 | 2.0 (0.7, 5.4) | 0.18 | 0.5 (0.1, 2.0) | 0.29 |
| Waist circumference (per 10 cm) | 1.3 (1.2, 1.5) | <0.0001 | 1.6 (1.3, 1.8) | <0.0001 | 1.4 (1.1, 1.7) | 0.0043 | 0.9 (0.7, 1.2) | 0.52 |
| Hypertension | 1.4 (0.9, 2.3) | 0.19 | 2.3 (0.9, 5.4) | 0.068 | 1.3 (0.5, 2.9) | 0.6 | 0.8 (0.3, 1.9) | 0.62 |
| Diabetes | 1.7 (1.2, 2.5) | 0.0018 | 3.2 (2.0, 5.2) | <0.0001 | 1.1 (0.5, 2.1) | 0.86 | 0.6 (0.2, 1.6) | 0.29 |
| Myocardial infarction | 2.6 (1.8, 3.8) | <0.0001 | 3.0 (1.8, 5.1) | <0.0001 | 3.8 (2.1, 6.8) | <0.0001 | 0.5 (0.1, 2.1) | 0.36 |
| Coronary revascularisation | 1.9 (1.4, 2.7) | 0.0002 | 2.0 (1.2, 3.4) | 0.0062 | 2.4 (1.3, 4.2) | 0.0034 | 1.1 (0.5, 2.6) | 0.83 |
| Stroke/TIA | 1.2 (0.8, 2.0) | 0.35 | 1.8 (1.0, 3.3) | 0.05 | 0.9 (0.3, 2.2) | 0.74 | 0.7 (0.2, 2.4) | 0.62 |
| PVD | 3.2 (1.9, 5.4) | <0.0001 | 1.7 (0.6, 4.7) | 0.3 | 4.6 (2.1, 10.2) | 0.0002 | 3.7 (1.3, 10.4) | 0.014 |
| AF | 2.5 (1.8, 3.7) | <0.0001 | 3.9 (2.4, 6.5) | <0.0001 | 1.1 (0.4, 2.5) | 0.92 | 2.4 (1.1, 5.2) | 0.031 |
| Pacemaker | 2.6 (1.2, 5.6) | 0.016 | 3.3 (1.2, 9.1) | 0.024 | 3.4 (1.1, 10.8) | 0.041 | No pacemakers |  |
| OSA | 2.1 (1.3, 3.3) | 0.0022 | 2.4 (1.3, 4.6) | 0.0072 | 2.4 (1.1, 5.1) | 0.021 | 0.8 (0.2, 3.3) | 0.73 |
| Current or former smoker | 1.4 (1.0, 1.9) | 0.04 | 1.1 (0.7, 1.8) | 0.65 | 1.8 (1.0, 3.2) | 0.035 | 1.4 (0.7, 2.8) | 0.3 |
| Alcohol >2 drinks/day | 1.2 (0.9, 1.8) | 0.24 | 0.7 (0.4, 1.3) | 0.26 | 1.5 (0.8, 2.8) | 0.16 | 2.2 (1.1, 4.3) | 0.024 |
| NT-proBNP quintile | 2.2 (1.9, 2.6) | <0.0001 | 2.4 (1.8, 3.1) | <0.0001 | 2.2 (1.7, 2.9) | <0.0001 | 1.8 (1.3, 2.5) | 0.0002 |
| eGFR (per 10 mL/min/1.73m2) | 0.83 (0.76, 0.91) | <0.0001 | 0.78 (0.69, 0.89) | 0.0002 | 0.86 (0.73, 1.02) | 0.078 | 0.89 (0.73, 1.09) | 0.27 |
| Haemoglobin (g/dL) | 0.86 (0.75, 0.99) | 0.031 | 0.69 (0.58, 0.83) | <0.0001 | 1.16 (0.90, 1.48) | 0.25 | 0.90 (0.69, 1.18) | 0.44 |
| log WCC (per doubling) | 1.7 (1.1, 2.7) | 0.028 | 3.8 (2.0, 7.2) | <0.0001 | 0.9 (0.5, 1.7) | 0.7 | 0.8 (0.3, 2.3) | 0.66 |
| log Platelets (per doubling) | 0.6 (0.4, 0.9) | 0.018 | 1.2 (0.6, 2.4) | 0.54 | 0.3 (0.2, 0.6) | 0.0004 | 0.4 (0.2, 0.9) | 0.03 |
| ß-blocker | 2.0 (1.4, 2.7) | <0.0001 | 2.8 (1.8, 4.5) | <0.0001 | 1.4 (0.8, 2.5) | 0.26 | 1.4 (0.7, 2.9) | 0.31 |
| ACE inhibitor | 1.4 (1.0, 1.9) | 0.049 | 1.1 (0.7, 1.8) | 0.74 | 1.6 (0.9, 2.7) | 0.11 | 1.8 (0.9, 3.4) | 0.093 |
| ARB | 0.9 (0.6, 1.2) | 0.39 | 1.3 (0.8, 2.1) | 0.23 | 0.6 (0.4, 1.1) | 0.12 | 0.6 (0.3, 1.2) | 0.12 |
| ACE inhibitor or ARB | 1.1 (0.8, 1.6) | 0.51 | 1.4 (0.8, 2.4) | 0.3 | 1.1 (0.6, 2.0) | 0.86 | 0.9 (0.4, 1.9) | 0.76 |
| CCB | 1.2 (0.9, 1.7) | 0.26 | 0.9 (0.5, 1.6) | 0.77 | 1.7 (1.0, 3.0) | 0.055 | 1.2 (0.6, 2.4) | 0.68 |
| Statin | 1.4 (1.0, 1.9) | 0.032 | 1.8 (1.1, 2.9) | 0.017 | 1.2 (0.7, 2.1) | 0.47 | 1.1 (0.5, 2.0) | 0.89 |
| Thiazide diuretic | 0.9 (0.7, 1.3) | 0.7 | 1.3 (0.8, 2.1) | 0.25 | 0.6 (0.3, 1.2) | 0.19 | 0.7 (0.3, 1.6) | 0.42 |
| Loop diuretic | 4.4 (2.7, 7.1) | <0.0001 | 6.9 (3.8, 12.4) | <0.0001 | 2.6 (0.9, 7.3) | 0.075 | 1.9 (0.5, 7.7) | 0.39 |
| Aspirin | 1.1 (0.8, 1.5) | 0.54 | 0.9 (0.6, 1.5) | 0.75 | 1.5 (0.9, 2.6) | 0.13 | 1.0 (0.5, 1.9) | 0.93 |
| NSAID | 1.9 (1.2, 2.9) | 0.0066 | 2.0 (1.0, 3.8) | 0.038 | 2.0 (0.9, 4.2) | 0.082 | 1.4 (0.5, 3.9) | 0.57 |
| Clopidogrel | 2.0 (1.2, 3.3) | 0.0046 | 2.4 (1.2, 4.7) | 0.0099 | 2.2 (1.0, 5.0) | 0.054 | 0.9 (0.2, 3.7) | 0.86 |
| Warfarin | 2.8 (1.7, 4.5) | <0.0001 | 4.3 (2.3, 7.8) | <0.0001 | 0.7 (0.2, 3.0) | 0.67 | 3.1 (1.2, 8.0) | 0.022 |

Univariate hazard ratios (HR) and 95% confidence intervals (CI) for risk factors for total incident heart failure (HF), HF with preserved (HFpEF) and reduced ejection fraction (HFrEF) and valvular HF (VHF). ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin II type 1 receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnoea; PP, pulse pressure; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack; WCC, white cell count. Alcohol >2 drinks/day refers to consumption of more than 2 standard drinks on any day. HRs were calculated using a semiparametric proportional hazards model for the subdistribution of competing risk, with non-HF related death and other categories of HF as competing risks.

**Supplementary Table 2.** Correlations between baseline characteristics of SCREEN-HF participants and baseline log NT-proBNP levels.

|  |  |  |
| --- | --- | --- |
|  | R | *P*-value |
| Age (years) | 0.433 | <0.0001 |
| SBP (mmHg) | 0.085 | <0.0001 |
| DBP (mmHg) | -0.127 | <0.0001 |
| PP (mmHg) | 0.194 | <0.0001 |
| log Heart rate (bpm) | -0.140 | <0.0001 |
| log BMI (kg/m2) | -0.090 | <0.0001 |
| Waist circumference (cm) | -0.091 | <0.0001 |
| eGFR (ml/min/1.73m2) | -0.221 | <0.0001 |
| Haemoglobin (g/dL) | -0.222 | <0.0001 |
| log WCC (x109/L) | 0.039 | 0.015 |
| Platelets (x109/L) | -0.053 | 0.001 |

Serum amino-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured in 3842 SCREEN-HF participants. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; PP, pulse pressure; SBP, systolic blood pressure; WCC, white cell count.

**Supplementary Table 3.** Associations between baseline categorical characteristics of SCREEN-HF participants and baseline NT-proBNP levels.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Characteristic present | | | Characteristic absent | | |  |
|  |  | n | NT-proBNP  (pmol/L) |  | n | NT-proBNP  (pmol/L) | *P*-value |
| Gender | Male | 2098 | 10 (5, 21) | Female | 1744 | 14 (8, 26) | <0.0001 |
| Hypertension | Present | 3292 | 12 (6, 23) | Absent | 550 | 13 (7, 26) | 0.049 |
| Diabetes | Present | 703 | 11 (5, 24) | Absent | 3139 | 12 (7, 24) | 0.013 |
| Myocardial infarction | Present | 390 | 18 (9, 40) | Absent | 3452 | 12 (6, 22) | <0.0001 |
| Coronary revascularization | Present | 575 | 18 (9, 35) | Absent | 3267 | 12 (6, 22) | <0.0001 |
| Stroke/TIA | Present | 420 | 15 (8, 34) | Absent | 3422 | 12 (6, 23) | <0.0001 |
| PVD | Present | 125 | 26 (13, 55) | Absent | 3717 | 12 (6, 23) | <0.0001 |
| AF | Present | 393 | 29 (14, 74) | Absent | 3449 | 11 (6, 21) | <0.0001 |
| Pacemaker | Present | 66 | 37 (15, 81) | Absent | 3776 | 12 (6, 23) | <0.0001 |
| OSA | Yes | 279 | 12 (5, 25) | No | 3563 | 12 (6, 24) | 0.17 |
| Smoker (current or former) | Smoker | 1889 | 12 (6, 24) | Non-smoker | 1953 | 13 (6, 23) | 0.56 |
| Alcohol >2 drinks/day | Yes | 762 | 11 (6, 22) | No | 3080 | 13 (6, 24) | 0.0076 |
| Medication | | | | | | | |
| ß-blocker | Yes | 888 | 20 (11, 40) | No | 2954 | 10 (6, 20) | <0.0001 |
| ACE inhibitor | Yes | 1187 | 12 (7, 24) | No | 2655 | 12 (6, 24) | 0.52 |
| ARB | Yes | 1804 | 12 (6, 23) | No | 2038 | 13 (7, 24) | <0.0001 |
| ACE inhibitor or ARB | Yes | 2849 | 12 (6, 23) | No | 992 | 14 (7, 26) | <0.0001 |
| CCB | Yes | 1048 | 13 (7, 26) | No | 2794 | 12 (6, 23) | 0.0001 |
| Statin | Yes | 1992 | 12 (6, 25) | No | 1850 | 12 (6, 23) | 0.55 |
| Thiazide diuretic | Yes | 1181 | 11 (6, 21) | No | 2661 | 13 (6, 25) | 0.0002 |
| Loop diuretic | Yes | 109 | 31 (15, 77) | No | 3733 | 12 (6, 23) | <0.0001 |
| Aspirin | Yes | 1601 | 13 (7, 25) | No | 2241 | 12 (6, 23) | 0.0063 |
| NSAID | Yes | 324 | 15 (7, 27) | No | 3518 | 12 (6, 23) | 0.0039 |
| Clopidogrel | Yes | 240 | 18 (9, 40) | No | 3602 | 12 (6, 23) | <0.0001 |
| Warfarin | Yes | 178 | 61 (22, 115) | No | 3664 | 12 (6, 22) | <0.0001 |

Serum amino-terminal pro-B-type natriuretic peptide (NT-proBNP), shown as median (interquartile range), was measured in 3842 SCREEN-HF participants. NT-proBNP levels had an approximate logarithmic distribution and the statistical significance of differences in NT-proBNP levels between the presence and absence of a characteristic was estimated with Student's t test of log NT-proBNP. ACE, angiotensin converting enzyme; AF, atrial fibrillation; ARB, angiotensin II type 1 receptor blocker; CCB, calcium channel blocker; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnoea; PVD, peripheral vascular disease; TIA, transient ischaemic attack. Alcohol >2 drinks/day refers to consumption of more than 2 standard drinks on any day.

**Supplementary Table 4.** Exploratory analyses of instances of non-proportional hazards with follow-up split into two periods.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | First time period | | | Second time period | |  |
| Period | HR (95% CI) | Events (n) | Period | HR (95% CI) | Events (n) |
| Association of male gender with HFpEF | ≤4.5 years | 0.9 (0.5, 1.8) | 36 | >4.5 years | 0.5 (0.3, 1.0) | 37 |
| Association of OSA with HFpEF | ≤4.5 years | 4.4 (2.1, 9.4) | 36 | >4.5 years | 0.8 (0.2, 3.4) | 37 |
| Association of haemoglobin with HFpEF | ≤5.2 years | 0.8 (0.7, 1.1) | 47 | >5.2 years | 0.5 (0.4, 0.6) | 26 |
| Association of PP with HFrEF | ≤3.2 years | 1.6 (1.3, 1.9) | 20 | >3.2 years | 1.0 (0.8, 1.3) | 33 |
| Association of diabetes with HFrEF | ≤3.2 years | 2.6 (1.0, 6.5) | 20 | >3.2 years | 0.5 (0.1, 1.5) | 33 |
| Association of loop diuretic therapy with HFrEF | ≤4.5 years | 5.1 (1.5, 17.1) | 25 | >4.5 years | 1.1 (0.1, 8.6) | 28 |
| Association of OSA with VHF | ≤4.5 years | 1.5 (0.3, 6.3) | 19 | >4.5 years | No OSA | 17 |

Univariate hazard ratios (HR) and 95% confidence intervals (CI) for risk factors for heart failure (HF) with preserved (HFpEF) and reduced ejection fraction (HFrEF) and valvular HF (VHF), with follow-up split into two periods. In these exploratory analyses, although hazards were non-proportional for the whole of follow-up, when follow-up was spilt into two periods, proportional hazards existed within each period. NT-proBNP, amino-terminal pro-B-type natriuretic peptide; OSA, obstructive sleep apnoea; PP, pulse pressure. HRs were calculated using a semiparametric proportional hazards model for the subdistribution of competing risk, with non-HF related death and other categories of HF as competing risks.

**Legends to figures**

**Supplementary Figure 1.** Incidence rate for total heart failure according to age group and gender. Error bars represent 95% confidence intervals. Poisson regression analysis demonstrated significant differences in HF incidence rate between the three age groups (*P*<0.01), but no difference between men and women.

**Supplementary Figure 2.** Kaplan-Meier survival curves after diagnosis of heart failure with preserved (HFpEF) and reduced ejection fraction (HFrEF) and valvular heart failure (VHF). X2=3.48, *P*=0.18 (log-rank test).