Supplementary material

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| **Leiden 85-plus Study** | **LiLACS NZ** | **Newcastle 85+ study** | **TOOTH** |
|  |  | Cross-sectional Analyses | Prospective Analyses |
| **Supplementary Figure 1**. Recruitment Flowchart and Schematic Representation of Data Samples Used in the Four Studies | | | |

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| **Supplementary Table 2.** Laboratory Methods and Analysers of the Four Studies | | | | |
|  | **Leiden 85-plus Study** | **LiLACS NZ** | **Newcastle 85+ Study** | **TOOTH** |
| Hemoglobin | Coulter Counter, Coulter Electronics, Hialeah, USA | Photometric measurement  (unicel dxh 800 coulter cellular analysis system, beckman coulter, inc. Chaska, mn, usa) | Tosoh Eurogenetics automated HLC-723G7 HPLC analyser | Flow cytometry using a semiconductor laser, a sheath flow DC detection method, SLS-HGB, RBC pulse height detection method (XE-2100, SYSMEX CORPORATION, Japan) |
| Serum Ferritin | Immunologic assay (E170, Roche,  Almere, the Netherlands). | Chemiluminescence (Cobas 8000, module c602, Roche Diagnostics, Manheim, Germany) | Immunoradiometric assay (Ferritin Mab; ICN Pharmaceuticals | CLEIA  (LUMIPULSEL2400, BFUJIREBIO INC., Japan) |
| Serum Vitamin B12 | Dual count solid phase no boil assay (diagnostic products corporation, los angeles, california, usa). | Chemiluminescence (unicel dxi 800 Immunoassay System, Beckman Coulter, Inc., Chaska, MN, USA) | Chemiluminescence  (microparticle immunoassay on an abbott architect analyser) | CLEIA  (UniCel DxI 800, Beckman Coulter, Inc., United States of America, USA) |
| Serum Folate/ Red Blood Cell Folate | Dual count solid phase no boil assay (diagnostic products corporation, los angeles, california, usa) | [**Red Blood Cell folate**]  Chemiluminescence (unicel dxi 800 Immunoassay System, Beckman  Coulter, Inc., Chaska, MN, USA) | [**Red Blood Cell folate**] chemiluminescence (Microparticle Immunoassay on an Abbott ARCHITECT analyser) | CLEIA  (UniCel DxI 800, Beckman Coulter, Inc., United States of America, USA) |
| Serum Creatinine | Jaffe method (Hitachi 747, Tokyo, Japan) | Automated HPLC Abbott Architect assay | Tosoh Eurogenetics automated HLC-723G7 HPLC analyser | Enzymatic method  (Bio Majesty (JCA-BM6010), JEOL Ltd., Japan) |
| C-reactive protein (CRP) | Immunoturbidimetric assay, Hitachi 747 automated analyser  (Hitachi, Tokyo, Japan) | Immunoturbidimetric assay (Roche, Auckland, New Zealand) | High-sensitivity immunoassay (cardiophase, Dade Behring, Deerfield, IL) in Behring Nephelometer. | Latex turbidimetric immunoassay (JCA-BM8060, JEOL Ltd., Japan) |

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| **Supplementary Table 3** Prevalence of Anaemia at Baseline, Depending on the Presence of Single and a Combination of Determinants | | | | | | | |
|  | | | Index group  N (%)a | Prevalence of anaemia at baseline in index group, N (%)ab | Prevalence of anaemia at baseline in reference group, N (%)c | Crude OR (95% CI)d | P value (chi squared test)e |
| **Iron deficiency** f | | |  |  |  |  |  |
|  | Leiden 85-plus Study | | 41/554 (7.4) | 22/41 (53.7) | 136/513 (26.5) | 3.21 (1.69 to 6.11) | <0.001 |
|  | LiLACS NZ (Māori) | | 5/165 (3.0) | 1/5 (20.0) | 35/160 (21.9) | 0.89 (0.10 to 8.25) | 0.92 |
|  | LilACS NZ (Non-Māori) | | 20/298 (6.7) | 6/20 (30.0) | 59/278 (21.2) | 1.59 (0.59 to 4.32) | 0.36 |
|  | Newcastle 85+ study | | 77/751 (10.3) | 44/77 (57.1) | 180/674 (26.7) | 3.66 (2.26 to 5.93) | <0.001 |
|  | TOOTH | | 56/344 (16.3) | 35/56 (62.5) | 131/288 (45.5) | 2.00 (1.11 to 3.60) | 0.02 |
| **Vitamin B12 deficiency** | | |  |  |  |  |  |
|  | Leiden 85-plus Study | | 85/553 (15.4) | 29/85 (34.1) | 128/468 (27.4) | 1.38 (0.84 to 2.25) | 0.20 |
|  | LiLACS NZ (Māori) | | 23/173 (13.3) | 4/23 (17.4) | 33/150 (22.0) | 0.75 (0.24 to 2.35) | 0.62 |
| … | LilACS NZ (Non-Māori) | | 48/285 (16.8) | 9/48 (18.8) | 56/237 (23.6) | 0.75 (0.34 to 1.63) | 0.46 |
|  | Newcastle 85+ study | | 131/751 (17.4) | 35/131 (26.7) | 188/620 (30.3) | 0.84 (0.55 to 1.28) | 0.41 |
|  | TOOTH | | 14/293 (4.8) | 13/14 (92.9) | 132/279 (47.3) | 14.48 (1.87 to 112.2) | <0.001 |
| **Folate deficiency** | | |  |  |  |  |  |
|  | Leiden 85-plus Study | | 42/553 (7.6) | 21/42 (50.0) | 136/511 (26.6) | 2.76 (1.46 to 5.21) | 0.002 |
|  | LiLACS NZ (Māori) | | 86/189 (45.5) | 25/86 (29.1) | 17/103 (16.5) | 2.07 (1.03 to 4.17) | 0.04 |
|  | LilACS NZ (Non-Māori) | | 131/326 (40.2) | 32/131 (24.4) | 36/195 (18.5) | 1.43 (0.83 to 2.45) | 0.19 |
|  | Newcastle 85+ study | | 26/752 (3.5) | 6/26 (23.1) | 218/726 (30.0) | 0.70 (0.28 to 1.77) | 0.45 |
|  | TOOTH | | 3/293 (1.0) | 1/3 (33.3) | 144/290 (49.7) | 0.51 (0.05 to 5.65) | 0.57 |
| **Low eGFR** | | |  |  |  |  |  |
|  | Leiden 85-plus Study | | 111/555 (20.0) | 47/111 (42.3) | 111/444 (25.0) | 2.20 (1.43 to 3.40) | <0.001 |
|  | LiLACS NZ (Māori) | | 37/204 (18.1) | 18/37 (48.6) | 26/167 (15.6) | 5.14 (2.38 to 11.08) | <0.001 |
|  | LilACS NZ (Non-Māori) | | 49/356 (13.8) | 23/49 (46.9) | 52/307 (16.9) | 4.34 (2.30 to 8.19) | <0.001 |
|  | Newcastle 85+ study | | 234/752 (31.1) | 108/234 (46.2) | 116/518 (22.4) | 2.97 (2.14 to 4.13) | <0.001 |
|  | TOOTH | | 21/345 (6.1) | 13/21 (61.9) | 154/324 (47.5) | 1.79 (0.72 to 4.45) | 0.20 |
| **High CRP** | | |  |  |  |  |  |
|  | Leiden 85-plus Study | | 191/555 (34.4) | 75/191 (39.3) | 83/364 (22.8) | 2.19 (1.50 to 3.20) | <0.001 |
|  | LiLACS NZ (Māori) | | 51/206 (24.8) | 19/51 (37.3) | 26/155 (16.8) | 2.95 (1.45 to 5.97) | 0.002 |
|  | LilACS NZ (Non-Māori) | | 86/356 (24.2) | 30/86 (34.9) | 45/270 (16.7) | 2.68 (1.55 to 4.63) | <0.001 |
|  | Newcastle 85+ study | | 220/751 (29.3) | 93/220 (42.3) | 131/531 (24.7) | 2.24 (1.60 to 3.12) | <0.001 |
|  | TOOTH | | 40/342 (11.7) | 26/40 (65.0) | 140/302 (46.4) | 2.15 (1.08 to 4.28) | 0.03 |
| **Sum of Abnormal Determinants**g | | | Index group  N (%) | Prevalence of anaemia at baseline in index group, N (%) | Prevalence of anaemia at baseline in reference group, N (%) | Crude odds ratio (95% CI) | P value (Logistic Regression)e |
| Leiden 85-plus Study | | 0 | 226/555 (40.7) | 36/226 (15.9) | Reference | 1 |  |
|  | | 1 | 208/555 (37.5) | 64/208 (30.8) | 36/226 (15.9) | 2.35 (1.48 to 3.72) | <0.001 |
|  | | 2 | 103/555 (18.6) | 45/103 (43.7) | 4.10 (2.42 to 6.94) | <0.001 |
|  | | 3 | 16/555 (2.9) | 12/16 (75.0) | 15.83 (4.83 to 51.86) | <0.001 |
|  | | 4 | 2/555 (0.4) | 1/2 (50.0) | 5.28 (0.32 to 86.33) | 0.243 |
|  | | 5 | 0/555 (0) | 0/0 | - | - |
| LiLACS NZ (Māori) | | 0 | 71/207 (34.3) | 8/71 (11.3) | Reference | 1 |  |
|  | | 1 | 85/207 (41.1) | 16/85 (18.8) | 8/71 (11.3) | 1.83 (0.73 to 4.56) | 0.20 |
|  | | 2 | 36/207 (17.4) | 12/36 (33.3) | 3.94 (1.43 to 10.82) | 0.01 |
|  | | 3 | 15/207 (7.2) | 9/15 (60.0) | 11.81 (3.32 to 41. 99) | <0.001 |
|  | | 4 | 0/207 (0) | 0/0 | - | - |
|  | | 5 | 0/207 (0) | 0/0 | - | - |
| LilACS NZ (Non-Māori) | | 0 | 121/357 (33.9) | 15/121 (12.4) | Reference | 1 |  |
|  | | 1 | 150/357 (42.0) | 23/150 (15.3) | 15/121 (12.4) | 1.28 (0.64 to 2.58) | 0.49 |
|  | | 2 | 76/357 (21.3) | 34/76(44.7) | 5.72 (2.83 to 11.58) | <0.001 |
|  | | 3 | 9/357 (2.5) | 3/9 (33.3) | 3.53 (0.80 to 15.64) | 0.10 |
|  | | 4 | 0/357 (0) | 0/0 | - h | - |
|  | | 5 | 1/357 (0.3) | 0/1 (0) | - | - |
| Newcastle 85+ study | | 0 | 262/752 (34.8) | 41/262 (15.6) | Reference | 1 |  |
|  | | 1 | 326/752 (43.4) | 103/326 (31.6) | 41/262 (15.6) | 2.49 (1.66 to 3.74) | <0.001 |
|  | | 2 | 132/752 (17.6) | 58/132 (43.9) | 4.23 (2.62 to 6.82) | <0.001 |
|  | | 3 | 30/752 (4.0) | 21/30 (70.0) | 12.58 (5.38 to 29.40) | <0.001 |
|  | | 4 | 2/752 (0.3) | 1/2 (50.0) | 5.39 (0.33 to 87.91) | 0.24 |
|  | | 5 | 0/752 (0) | 0/0 | - | - |
| TOOTH | | 0 | 229/345 (66.4) | 95/229 (41.5) | Reference | 1 |  |
|  | | 1 | 100/345 (29.0) | 58/100 (58.0) | 95/229 (41.5) | 1.95 (1.21 to 3.14) | 0.006 |
|  | | 2 | 14/345 (4.1) | 12/14 (85.7) | 8.46 (1.85 to 38.69) | 0.006 |
|  | | 3 | 2/345 (0.6) | 2/2 (100.0) | - | - |
|  | | 4 | 0/345 (0) | 0/0 (0) | - | - |
|  | | 5 | 0/345 (0) | 0/0 (0) | - | - |
| **Combination of Determinants**g | | | Index group  N (%) | Prevalence of anaemia at baseline in index group, N (%) | Prevalence of anaemia at baseline in reference group, N (%) | Crude odds ratio (95% CI) | P value (chi squared test) |
|  | Leiden 85-plus Study | | 121/555 (21.8) | 58/121 (47.9) | 100/434 (23.0) | 3.08 (2.02 to 4.68) | <0.001 |
|  | LiLACS NZ (Māori) | | 51/207 (24.6) | 21/51 (41.2) | 24/156 (15.4) | 3.85 (1.90 to 7.81) | <0.001 |
|  | LilACS NZ (Non-Māori) | | 86/357 (24.1) | 37/86 (43.0) | 38/271 (14.0) | 4.63 (2.68 to 8.01) | <0.001 |
|  | Newcastle 85+ study | | 164/752 (21.8) | 80/164 (48.8) | 144/588 (24.5) | 2.94 (2.05 to 4.21) | <0.001 |
|  | TOOTH | | 16/345 (4.6) | 14/16 (87.5) | 153/329 (46.5) | 8.05 (1.80 to 36.0) | 0.001 |
| Abbreviations: OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.  a Index group = iron deficiency, vitamin B12 deficiency, folate deficiency, low eGFR, high CRP; 1,2,3,4,5 combination of abnormal determinants; ≥2 combination of abnormal determinants.  b Population with anaemia within index group.  c Reference group = normal ferritin, normal vitamin B12, normal folate, normal eGFR, normal CRP; 0 combination of abnormal determinants; 0-1 combination of abnormal determinants. Population with anaemia within reference group.  d Crude (model 1). Results were presented as odds ratio with a 95% confidence interval.  e P value was derived from chi-square test except sum of combination of abnormal determinants.  f Iron deficiency was defined as ferritin <20 μg/L for men, <15 μg/L for women; vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) or red blood cell folate <317 nmol/L (LiLACS NZ) and <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation; high CRP was >5 mg/L. Conversion factors: to convert serum vitamin B12 to picograms per milliliter, divide by 0.7378; to convert folate to nanograms per milliliter, divide by 2.265.  g All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP.  h A population size of zero led to an inestimable odds ratio and p value. | | | | | | | |

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| **Supplementary Table 4.** Cross-sectional Results: Single and a Combination of Determinants of Anaemia in Association with the Presence of Anaemia at Baseline in the Four Studies (Crude and Two Adjusted Models)a | | | | | | | |
|  | |  | Leiden 85-plus Study (N=555) | LiLACS NZ  Māori (N=207) | LiLACS NZ  Non-Māori (N=357) | Newcastle 85+ study  (N=752) | TOOTH  (N=345) |
|  | |  | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Single Determinantsb |  | | | | | | |
| Iron Deficiency | | Model 1c | 3.21 (1.69 to 6.11) | 0.89 (0.10 to 8.25) | 1.59 (0.59 to 4.32) | 3.66 (2.26 to 5.93) | 2.00 (1.11 to 3.60) |
|  | | Model 2d | 2.95 (1.50 to 5.80) | 0.88 (0.09 to 8.99) | 1.59 (0.56 to 4.50) | 4.13 (2.52 to 6.78) | 2.15 (1.16 to 3.96) |
|  | | Model 3e | 2.99 (1.51 to 5.89) | 0.87 (0.08 to 9.02) | 1.59 (0.56 to 4.52) | 4.19 (2.54 to 6.91) | 2.15 (1.16 to 3.97) |
| Vitamin B12 Deficiency | | Model 1 | 1.38 (0.84 to 2.25) | 0.75 (0.24 to 2.35) | 0.75 (0.34 to 1.63) | 0.84 (0.55 to 1.28) | 14.5 (1.87 to 112) |
|  | | Model 2 | 1.48 (0.89 to 2.47) | 0.89 (0.27 to 2.97) | 0.80 (0.35 to 1.79) | 0.88 (0.57 to 1.36) | 12.5 (1.59 to 98.3) |
|  | | Model 3 | 1.48 (0.88 to 2.46) | 0.90 (0.27 to 3.01) | 0.78 (0.35 to 1.77) | 0.91 (0.59 to 1.41) | 12.7 (1.61 to 99.5) |
| Folate Deficiency | | Model 1 | 2.76 (1.46 to 5.21) | 2.07 (1.03 to 4.17) | 1.43 (0.83 to 2.45) | 0.70 (0.28 to 1.77) | 0.51 (0.05 to 5.65) |
|  | | Model 2 | 2.06 (1.05 to 4.05) | 2.55 (1.20 to 5.42) | 1.26 (0.71 to 2.22) | 0.64 (0.24 to 1.69) | 0.19 (0.01 to 3.36) |
|  | | Model 3 | 2.05 (1.04 to 4.04) | 2.55 (1.20 to 5.41) | 1.28 (0.72 to 2.26) | 0.72 (0.27 to 1.89) | 0.17 (0.01 to 3.33) |
| Low eGFRb | | Model 1 | 2.20 (1.43 to 3.40) | 5.14 (2.38 to 11.08) | 4.34 (2.30 to 8.19) | 2.97 (2.14 to 4.13) | 1.79 (0.72 to 4.45) |
|  | | Model 2 | 2.38 (1.51 to 3.76) | 5.73 (2.46 to 13.37) | 4.39 (2.23 to 8.66) | 3.16 (2.23 to 4.46) | 1.66 (0.65 to 4.22) |
|  | | Model 3 | 2.44 (1.54 to 3.88) | 6.96 (2.79 to 17.36) | 4.20 (2.12 to 8.32) | 3.06 (2.16 to 4.34) | 1.67 (0.65 to 4.25) |
| High CRP | | Model 1 | 2.19 (1.50 to 3.20) | 2.95 (1.45 to 5.97) | 2.68 (1.55 to 4.63) | 2.24 (1.60 to 3.12) | 2.15 (1.08 to 4.28) |
|  | | Model 2 | 1.97 (1.31 to 2.95) | 2.14 (0.99 to 4.61) | 2.64 (1.49 to 4.68) | 2.01 (1.43 to 2.83) | 1.94 (0.94 to 4.02) |
|  | | Model 3 | 2.02 (1.34 to 3.05) | 2.23 (1.02 to 4.90) | 2.72 (1.52 to 4.85) | 1.97 (1.40 to 2.78) | 1.95 (0.94 to 4.04) |
| Increase per Additional Abnormal Determinantf | | Model 1 | 2.10 (1.67 to 2.63) | 2.21 (1.51 to 3.22) | 2.04 (1.49 to 2.80) | 2.10 (1.72 to 2.56) | 2.26 (1.52 to 3.35) |
| Model 2 | 2.04 (1.61 to 2.59) | 2.27 (1.50 to 3.41) | 1.94 (1.40 to 2.68) | 2.12 (1.73 to 2.59) | 2.16 (1.43 to 3.25) |
| Model 3 | 2.06 (1.62 to 2.63) | 2.36 (1.55 to 3.60) | 1.95 (1.41 to 2.70) | 2.11 (1.72 to 2.58) | 2.17 (1.44 to 3.27) |
| ≥2 Combination of Determinantsf | | Model 1 | 3.08 (2.02 to 4.68) | 3.85 (1.90 to 7.81) | 4.63 (2.68 to 8.01) | 2.94 (2.05 to 4.21) | 8.05 (1.80 to 36.0) |
|  | | Model 2 | 2.93 (1.87 to 4.58) | 4.16 (1.95 to 8.89) | 4.31 (2.43 to 7.63) | 3.12 (2.15 to 4.52) | 6.48 (1.42 to 29.4) |
|  | | Model 3 | 2.97 (1.89 to 4.65) | 4.60 (2.08 to 10.13) | 4.32 (2.43 to 7.69) | 3.12 (2.14 to 4.54) | 6.60 (1.45 to 30.1) |
| Abbreviations: OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.  a LiLACS NZ contained two cohorts: Māori and non-Māori population; TOOTH: since not all determinants were collected at baseline, 3-year follow-up was defined as baseline, and 6-year follow-up as follow-up data.  b Iron deficiency was defined as ferritin <20 μg/L for men, <15 μg/L for women; vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) or red blood cell folate<317 nmol/L (LiLACS NZ)and <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation; high CRP was >5 mg/L. Conversion factors: to convert serum vitamin B12 to picograms per milliliter, divide by 0.7378; to convert folate to nanograms per milliliter, divide by 2.265.  c Crude model. Results were presented as odds ratio with a 95% confidence interval.  d Adjusted for age (except Leiden 85-plus Study having all participants aged 85 years old), sex, institutionalisation (except TOOTH which served as an exclusion criteria) and smoking.  e Fully adjusted model: adjusted for age, sex, institutionalisation, smoking, and ≥2 multi-morbidity. Multi-morbidity was composed of stroke, coronary heart disease (CHD), cancer and diabetes. It was stratified into 0 to 1 or 2 and above as a binary variable. Leiden 85-plus Study: sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke, coronary heart disease (CHD) excluding stroke, cancer, diabetes]; LiLACS NZ: age, sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke (cerebrovascular accident (CVA), cardiovascular disease (CVD) excluding stroke, cancer, diabetes]; Newcastle 85+ study: age, sex, institutionalisation, smoking, ≥2 multi-morbidity (CVA, combined cardiac disease excluding CVA, cancer, diabetes); TOOTH: age, sex, smoking, ≥2 multi-morbidity (stroke , coronary heart disease (CHD), cancer, diabetes).  f All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP. | | | | | | | |

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| **Supplementary Table 5** The prevalence of 0, 1, 2, 3, 4 and 5 (out of 5) abnormal determinants for participants with and without anemia at baseline in four studies ab | | | | | | | | | | | | | | | |
|  | Leiden 85-plus Study  N=555 | |  | LiLACS NZ (Māori)  N=207 | |  | LilACS NZ (Non-Māori) N=356 | |  | Newcastle 85+ study  N=752 | |  | TOOTH  N=345 | |  |
|  | Anaemia at baselinec  n=158  N (%) | No anaemia at baselined  n=397 | P value (Chi square test) e | Anaemia at baseline  n=45 | No anaemia at baseline  n=162 | P value (Chi square test) | Anaemia at baseline  n=75 | No anaemia at baseline  n=282 | P value (Chi square test) | Anaemia at baseline  n=224 | No anaemia at baseline  n=528 | P value (Chi square test) | Anaemia at baseline  n=167 | No anaemia at baseline  n=178 | P value (Chi square test) |
| **Sum of Abnormal Determinants** | | | | |  |  |  |  |  |  |  |  |  |  |  |
| 0 | 36 (22.8) | 190 (47.9) | <0.001 | 8 (17.8) | 63 (38.9) | <0.001 | 15 (20.0) | 106 (37.7) | <0.001 | 41 (18.3) | 221 (41.9) | <0.001 | 95 (56.9) | 134 (75.3) | <0.001 |
| 1 | 64 (40.5) | 144 (36.3) | 16 (35.6) | 69 (42.6) | 23 (30.7) | 126 (44.8) | 103 (46.0) | 223 (42.2) | 58 (34.7) | 42 (23.6) |  |
| 2 | 45 (28.5) | 58 (14.6) | 12 (26.7) | 24 (14.8) | 34 (45.3) | 42 (14.9) | 58 (25.9) | 74 (14.0) | 12 (7.2) | 2 (1.1) |  |
| 3 | 12 (7.6) | 4 (14.6) | 9 (20.0) | 6 (3.7) | 3 (4.0) | 6 (2.1) | 21 (9.4) | 9 (1.7) | 2 (1.2) | 0 |  |
| 4 | 1 (0.6) | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (0.4) | 1 (0.2) | 0 | 0 |  |
| 5 | 0 | 0 | 0 | 0 | 0 | 1 (0.4) | 0 | 0 | 0 | 0 |  |
| **≥2 Combination of Determinants** | | | |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 58 (36.7) | 63 (15.9) | <0.001 | 21 (46.7) | 30 (18.5) | <0.001 | 37 (49.3) | 49 (17.4) | <0.001 | 80 (35.7) | 84 (15.9) | <0.001 | 14 (8.4) | 2 (1.1) | 0.001 |
| a All variables were presented as number (percentage).  b All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP.  c Within population with anaemia at baseline.  d Within population without anaemia at baseline.  e P value was derived from chi-square test. | | | | | | | | | | | | | | |  |

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| **Supplementary Table 6.** Incidence of Anaemia from Age 85 Years Onwards, depending on the presence of single and a combination of determinants | | | | | | | | |
|  | | | Index group  N (%)a | | Incidence of anaemia in index group,  per 100 py (95%CI)ab | Incidence of anemia in reference group, per 100 py (95%CI)c | Crude HR  (95% CI)d | P value (Cox regression)e |
| **Iron deficiencyf** | | |  | |  |  |  |  |
|  | Leiden 85-plus Study | | 17/360 (4.7) | | 11.8 (5.0 to 18.5) | 7.8 (2.3 to 13.3) | 1.45 (0.63 to 3.31) | 0.38 |
|  | Newcastle 85+ study | | 25/418 (6.0) | | 30.4 (19.6 to 41.2) | 10.8 (4.4 to 17.2) | 2.38 (1.34 to 4.26) | 0.003 |
|  | TOOTH | | 13/97 (13.4) | | 12.1 (5.3 to 18.9) | 13.9 (6.6 to 21.2) | 0.89 (0.31 ro 2.54) | 0.83 |
| **Vitamin B12 deficiency** | | |  | |  |  |  |  |
|  | Leiden 85-plus Study | | 53/360 (14.7) | | 8.8 (3.0 to 14.7) | 7.8 (2.3 to 13.3) | 1.12 (0.66 to 1.92) | 0.67 |
|  | Newcastle 85+ study | | 74/418 (17.7) | | 15.4 (7.7. to 23.1) | 10.9 (4.4 to 17.4) | 1.38 (0.88 to 2.16) | 0.16 |
|  | TOOTH | | 1/82 (1.2) | | 0 (-)h | 13.9 (6.6 to 21.2) | 0.05 (-)h | 0.70 |
| **Folate deficiency** | | |  | |  |  |  |  |
|  | Leiden 85-plus Study | | 19/360 (5.3) | | 25.6 (15.7 to 35.6) | 7.4 (2.1 to 12.7) | 3.01 (1.56 to 5.81) | 0.001 |
|  | Newcastle 85+ study | | 14/418 (3.3) | | 6.3 (1.4 to 11.3) | 11.9 (5.1 to 18.6) | 0.55 (0.14 to 2.23) | 0.40 |
|  | TOOTH | | 2/82 (2.4) | | 22.2 (13.0 to 31.5) | 13.5 (6.3 to 20.7) | 1.48 (0.20 to 10.90) | 0.70 |
| **Low eGFR** | | |  | |  |  |  |  |
|  | Leiden 85-plus study | | 54/361 (15.0) | | 8.2 (2.6 to 13.9) | 7.9 (2.4 to 13.4) | 1.02 (0.58 to 1.80) | 0.94 |
|  | Newcastle 85+ study | | 105/418 (25.1) | | 19.7 (11.0 to 28.4) | 9.4 (3.4 to 15.4) | 1.92 (1.30 to 2.83) | 0.001 |
|  | TOOTH | | 3/97 (3.1) | | 66.7 (50.7 to 82.7) | 12.7 (5.7 to 19.6) | 3.19 (0.98 to 10.36) | 0.05 |
| **High CRP** | | |  | |  |  |  |  |
|  | Leiden 85-plus study | | 97/361 (26.9) | | 11.3 (4.7 to 17.9) | 6.9 (1.8 to 12.1) | 1.58 (1.04 to 2.40) | 0.03 |
|  | Newcastle 85+ study | | 92/417 (22.1) | | 14.8 (7.3 to 22.4) | 10.9 (4.4 to 17.4) | 1.31 (0.86 to 2.00) | 0.21 |
|  | TOOTH | | 6/96 (6.3) | | 22.2 (13.0 to 31.5) | 13.3 (6.2 to 20.5) | 1.50 (0.46 to 3.92) | 0.50 |
| **Increase per Additional Abnormal Determinantg** | | | | | |  |  |  |
| Leiden 85-plus study | | 0 | | 180/361 (49.9) | 6.1 (1.3 to 10.9) | Reference | 1 |  |
|  | | 1 | | 128/361 (35.5) | 9.1 (3.2 to 15.0) | 6.1 (1.3 to 10.9) | 1.45 (0.93 to 2.26) | 0.10 |
|  | | 2 | | 48/361 (13.3) | 13.6 (6.4 to 20.9) | 2.09 (1.20 to 3.64) | 0.01 |
|  | | 3 | | 4/361 (1.1) | 14.3 (6.9 to 21.7) | 2.24 (0.54 to 9.27) | 0.27 |
|  | | 4 | | 1/361 (0.3) | 0 (-) | - | - |
|  | | 5 | | 0/361 (0) | 0 (-) | - | - |
| Newcastle 85+ study | | 0 | | 179/418 (42.8) | 7.0 (1.8 to 12.2) | Reference | 1 |  |
|  | | 1 | | 176/418 (42.1) | 13.6 (6.4 to 20.9) | 7.0 (1.8 to 12.2) | 1.84 (1.17 to 2.88) | 0.008 |
|  | | 2 | | 55/418 (13.2) | 22.1 (12.9 to 31.3) | 2.76 (1.60 to 4.75) | <0.001 |
|  | | 3 | | 8/418 (1.9) | 24.2 (14.6 to 33.9) | 3.07 (1.08 to 8.71) | 0.035 |
|  | | 4 | | 0/418 (0) | 0 (-) | - | - |
|  | | 5 | | 0/418 (0) | 0 (-) | - | - |
| TOOTH | | 0 | | 73/97 (75.3) | 12.5 (5.5 to 19.4) | Reference | 1 |  |
|  | | 1 | | 23/97 (23.7) | 16.2 (8.3 to 24.1) | 12.5 (5.5 to 19.4) | 1.24 (0.58 to 2.68) | 0.58 |
|  | | 2 | | 1/97 (1.0) | 66.7 (50.7 to 82.7) | 3.17 (0.43 to 23.5) | 0.26 |
|  | | 3 | | 0/97 (0) | 0 (-) | - | - |
|  | | 4 | | 0/97 (0) | 0 (-) | - | - |
|  | | 5 | | 0/97 (0) | 0 (-) | - | - |
|  | | |  | |  |  |  |  |
| **Combination of Determinantsg** | | | | |  |  |  |  |
|  | Leiden 85-plus study | | 53/361 (14.7) | | 13.2 (6.1 to 20.4) | 7.2 (2.0 to 12.5) | 1.74 (1.07 to 2.85) | 0.03 |
|  | Newcastle 85+ study | | 63/418 (15.1) | | 22.4 (13.1 to 31.6) | 10.1 (3.9 to 16.3) | 1.99 (1.29 to 3.07) | 0.002 |
|  | TOOTH | | 1/97 (1.0) | | 66.7 (50.7 to 82.7) | 13.3 (6.2 to 20.5) | 3.00 (0.41 to 21.95) | 0.28 |
| Abbreviations: py, person-years; HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.  a Index group = iron, vitamin B12, folate deficiency, low eGFR, high CRP; 1,2,3,4,5 combination of abnormal determinants; ≥2 combination of abnormal determinants.  b Population who developed anaemia during follow-up within index group. Results were presented as per 100 person-years with 95% confidence interval.  c Reference group = normal ferritin, normal vitamin B12, normal folate, normal eGFR, normal CRP; 0 combination of abnormal determinants; 0-1 combination of abnormal determinants. Population who developed anaemia during follow-up within reference group.  d Crude (model 1) from cox regression. Results were presented as hazard ratio with a 95% confidence interval.  e P value was derived from cox regression.  f Iron deficiency was defined as ferritin <20 μg/L for men, <15 μg/L for women; vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) and <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation; high CRP was >5 mg/L. Conversion factors: to convert serum vitamin B12 to picograms per milliliter, divide by 0.7378; to convert folate to nanograms per milliliter, divide by 2.265.  g LiLACS NZ did not have follow-up data for hemoglobin; TOOTH: since not all determinants were collected at baseline, 3-year follow-up was defined as baseline, and 6-year follow-up as follow-up data. All three studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP.  h A population size of zero led to an inestimable hazard ratio and p value. | | | | | | | | |

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| **Supplementary Table 7.** Prospective Results: Single and a Combination of Determinants at Baseline in Association with the Onset of Anaemia during Follow-up in Three Studies (Crude and Two Adjusted Models)a | | | | |
|  |  | Leiden 85-plus Study (N=361) | Newcastle 85+ study (N=418) | TOOTH  (N=97) |
|  | | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| Single Determinantsb | |  |  |  |
| Iron Deficiency | Model 1c | 1.45 (0.63 to 3.31) | 2.38 (1.34 to 4.26) | 0.89 (0.31 to 2.54) |
|  | Model 2d | 1.47 (0.64 to 3.36) | 2.40 (1.34 to 4.30) | 0.88 (0.31 to 2.53) |
|  | Model 3e | 1.48 (0.64 to 3.40) | 2.41 (1.35 to 4.32) | 0.88 (0.30 to 2.53) |
| Vitamin B12 Deficiency | Model 1 | 1.12 (0.66 to 1.92) | 1.38 (0.88 to 2.16) | 0.05 (-g) |
|  | Model 2 | 1.03 (0.59 to 1.79) | 1.33 (0.84 to 2.10) | -g |
|  | Model 3 | 1.03 (0.59 to 1.79) | 1.35 (0.85 to 2.13) | - |
| Folate Deficiency | Model 1 | 3.01 (1.56 to 5.81) | 0.55 (0.14 to 2.23) | 1.48 (0.20 to 10.9) |
|  | Model 2 | 2.83 (1.45 to 5.51) | 0.54 (0.13 to 2.21) | 1.18 (0.11 to 12.6) |
|  | Model 3 | 2.84 (1.45 to 5.54) | 0.56 (0.14 to 2.30) | 1.20 (0.11 to 12.9) |
| Low eGFR | Model 1 | 1.02 (0.58 to 1.80) | 1.92 (1.30 to 2.83) | 3.19 (0.98 to 10.4) |
|  | Model 2 | 1.09 (0.61 to 1.94) | 2.00 (1.34 to 2.98) | 2.39 (0.68 to 8.40) |
|  | Model 3 | 1.09 (0.61 to 1.94) | 1.97 (1.32 to 2.94) | 2.41 (0.68 to 8.52) |
| High CRP | Model 1 | 1.58 (1.04 to 2.40) | 1.31 (0.86 to 2.00) | 1.50 (0.46 to 4.92) |
|  | Model 2 | 1.54 (1.00 to 2.39) | 1.28 (0.83 to 1.97) | 1.45 (0.42 to 4.95) |
|  | Model 3 | 1.56 (1.00 to 2.42) | 1.27 (0.83 to 1.96) | 1.45 (0.42 to 5.00) |
| Increase per Additional Abnormal Determinantf | Model 1 | 1.34 (1.07 to 1.69) | 1.58 (1.26 to 1.97) | 1.38 (0.71 to 2.70) |
| Model 2 | 1.35 (1.06 to 1.73) | 1.57 (1.25 to 1.98) | 1.28 (0.65 to 2.53) |
| Model 3 | 1.35 (1.06 to 1.73) | 1.58 (1.25 to 1.98) | 1.28 (0.65 to 2.53) |
| ≥2 Combination of Determinantsf | Model 1 | 1.74 (1.07 to 2.85) | 1.99 (1.29 to 3.07) | 3.00 (0.41 to 22.0) |
| Model 2 | 1.86 (1.12 to 3.11) | 2.01 (1.30 to 3.12) | 1.97 (0.25 to 15.4) |
|  | Model 3 | 1.87 (1.12 to 3.12) | 2.02 (1.30 to 3.13) | 1.98 (0.25 to 15.5) |
| Abbreviations: HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein.  a TOOTH: since not all determinants were collected at baseline, 3-year follow-up was defined as baseline, and 6-year follow-up as follow-up data.  b Iron deficiency was defined as ferritin <20 μg/L for men, <15 μg/L for women; vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) or <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation. High CRP was >5 mg/L. Conversion factors: to convert serum vitamin B12 to picograms per milliliter, divide by 0.7378; to convert folate to nanograms per milliliter, divide by 2.265.  c Crude model. Results were presented as hazard ratio with a 95% confidence interval.  d Adjusted for age (except Leiden 85+ Study having all participants aged 85 years old), sex, institutionalisation (except TOOTH which served as an exclusion criteria) and smoking.  e Fully adjusted model: adjusted for age, sex, institutionalisation, smoking, and ≥2 multi-morbidity. Multi-morbidity was composed of stroke, coronary heart disease (CHD), cancer and diabetes. It was stratified into 0 to 1 or 2 and above as a binary variable. Leiden 85-plus Study: sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke, coronary heart disease (CHD) excluding stroke, cancer, diabetes]; Newcastle 85+ study: age, sex, institutionalisation, smoking, ≥2 multi-morbidity (CVA, combined cardiac disease excluding CVA, cancer, diabetes); TOOTH: age, sex, smoking, ≥2 multi-morbidity (stroke , coronary heart disease (CHD), cancer, diabetes).  f All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP.  g A population size of zero led to an inestimable hazard ratio. | | | | |

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| **Supplementary Table 8** The prevalence of iron deficiency and the combination of abnormal determinants at baseline in the four studies using two different cut-offs for serum ferritin to define iron deficiencyab | | | | | | | | | | |
|  | **Serum Ferritin <15 μg/L (women), <20 μg/L (men)** | | | | | **Serum Ferritin <50 μg/L** | | | | |
|  | Leiden 85-plus (N=555) | LiLACS NZ  Māori  (N=207) | LiLACS NZ  Non-Māori (N=357) | Newcastle 85+  (N=752) | TOOTH  (N=345) | Leiden 85-plus (N=555) | LiLACS NZ  Māori  (N=207) | LiLACS NZ  Non-Māori (N=357) | Newcastle 85+  (N=752) | TOOTH  (N=345) |
| **Iron Deficiency** | |  |  |  |  |  |  |  |  |  |
|  | 41/554 (7.4) | 5/165 (3.0) | 20/298 (6.7) | 77/751 (10.3) | 56/344 (16.3) | 190/554 (34.3) | 30 /165 (18.2) | 67/298 (22.5) | 314 (41.8) | 162/344 (47.1) |
| **Sum of Combination of Abnormal Determinants**c | | | |  |  |  |  |  |  |  |
| 0 | 226 (40.7) | 71 (34.3) | 121 (33.9) | 262 (34.8) | 229/345 (66.4) | 156 (28.1) | 61 (29.5) | 104 (29.1) | 161 (21.4) | 148 (42.9) |
| 1 | 208 (37.5) | 85 (41.1) | 150 (42.0) | 326 (43.4) | 100 (29.0) | 225 (40.5) | 84 (40.6) | 149 (41.7) | 324 (43.1) | 158 (45.8) |
| 2 | 103 (18.6) | 36 (17.4) | 76 (21.3) | 132 (17.6) | 14 (4.1) | 135 (24.3) | 43 (20.8) | 84 (23.5) | 209 (27.8) | 36 (10.4) |
| 3 | 16 (2.9) | 15 (7.2) | 9 (2.5) | 30 (4.0) | 2 (0.6) | 32 (5.8) | 19 (9.2) | 17 (4.8) | 49 (6.5) | 2 (0.6) |
| 4 | 2 (0.4) | 0 | 0 | 2 (0.3) | 0 | 7 (1.3) | 0 | 2 (0.6) | 9 (1.2) | 1 (0.3) |
| 5 | 0 | 0 | 1 (0.3) | 0 | 0 | 0 | 0 | 1 (0.3) | 0 | 0 |
| **Combination of Determinants (≥2)** | | |  |  |  |  |  |  |  |  |
|  | 121 (21.8) | 51 (24.6) | 86 (24.1) | 164 (21.8) | 16 (4.6) | 174 (31.4) | 62 (30.0) | 104 (29.1) | 267(35.5) | 39 (11.3) |
| a Variables were presented as number (percentage).  b LiLACS NZ contained two cohorts: Māori and non-Māori population.  c All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP. Vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) or red blood cell folate <317 nmol/L (LiLACS NZ), <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation. High CRP was >5 mg/L. | | | | | | | | | | |

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| **Supplementary Table 9** Cross-sectional results: the association between iron deficiency, using two cut-offs for ferritin concentration, and the presence of anaemia at baseline in the four studies ab | | | | | | | | | | | |
|  |  | Serum Ferritin <15 μg/L (women), <20 μg/L (men) | | | | | Serum Ferritin <50 μg/L | | | | |
|  |  | Leiden 85-plus (N=555) | LiLACS NZ  Māori  (N=207) | LiLACS NZ  Non-Māori (N=357) | Newcastle 85+  (N=752) | TOOTH  (N=345) | Leiden 85-plus (N=555) | LiLACS NZ  Māori  (N=207) | LiLACS NZ  Non-Māori (N=357) | Newcastle 85+  (N=752) | TOOTH  (N=345) |
| **Iron Deficiency** | | |  |  |  |  |  |  |  |  |  |
|  | Model 1c | 3.21 (1.69 to 6.11) | 0.89 (0.10 to 8.25) | 1.59 (0.59 to 4.32) | 3.66 (2.26 to 5.93) | 2.00 (1.11 to 3.60) | 1.70 (1.16 to 2.48) | 0.88 (0.33 to 2.34) | 0.93 (0.48 to 1.82) | 1.41 (1.03 to 1.94) | 1.38 (0.90 to 2.11) |
|  | Model 2d | 2.95 (1.50 to 5.80) | 0.88 (0.09 to 8.99) | 1.59 (0.56 to 4.50) | 4.13 (2.52 to 6.78) | 2.15 (1.16 to 3.96) | 2.12 (1.40 to 3.19) | 1.12 (0.40 to 3.14) | 1.03 (0.52 to 2.07) | 1.69 (1.21 to 2.37) | 1.57 (1.01 to 2.46) |
|  | Model 3e | 2.99 (1.51 to 5.89) | 0.87 (0.08 to 9.02) | 1.59 (0.56 to 4.52) | 4.19 (2.54 to 6.91) | 2.15 (1.16 to 3.97) | 2.12 (1.40 to 3.20) | 1.12 (0.40 to 3.14) | 1.03 (0.51 to 2.06) | 1.63 (1.16 to 2.30) | 1.57 (1.00 to 2.46) |
| **Increase per Additional Abnormal Determinant** | | | | |  |  |  |  |  |  |  |
|  | Model 1c | 2.10 (1.67 to 2.63) | 2.21 (1.51 to 3.22) | 2.04 (1.49 to 2.80) | 2.10 (1.72 to 2.56) | 2.26 (1.52 to 3.35) | 1.95 (1.58 to 2.41) | 2.10 (1.45 to 3.04) | 1.76 (1.32 to 2.34) | 1.80 (1.50 to 2.16) | 1.71 (1.24 to 2.35) |
|  | Model 2 | 2.04 (1.61 to 2.59) | 2.27 (1.50 to 3.41) | 1.94 (1.40 to 2.68) | 2.12 (1.73 to 2.59) | 2.16 (1.43 to 3.25) | 2.03 (1.62 to 2.54) | 2.27 (1.51 to 3.42) | 1.74 (1.29 to 2.34) | 1.88 (1.56 to 2.27) | 1.71 (1.23 to 2.38) |
|  | Model 3 | 2.06 (1.62 to 2.63) | 2.36 (1.55 to 3.60) | 1.95 (1.41 to 2.70) | 2.11 (1.72 to 2.58) | 2.17 (1.44 to 3.27) | 2.05 (1.63 to 2.57) | 2.38 (1.57 to 3.63) | 1.75 (1.30 to 2.36) | 1.86 (1.53 to 2.25) | 1.72 (1.23 to 2.39) |
| **Combination of Determinants (≥2)** | | | |  |  |  |  |  |  |  |  |
|  | Model 1 | 3.08 (2.02 to 4.68) | 3.85 (1.90 to 7.81) | 4.63 (2.68 to 8.01) | 2.94 (2.05 to 4.21) | 8.05 (1.80 to 36.0) | 3.06 (2.08 to 4.50) | 3.30 (1.66 to 6.55) | 3.36 (1.98 to 5.71) | 2.10 (1.53 to 2.90) | 4.11 (1.89 to 8.95) |
|  | Model 2 | 2.93 (1.87 to 4.58) | 4.16 (1.95 to 8.89) | 4.31 (2.43 to 7.63) | 3.12 (2.15 to 4.52) | 6.48 (1.42 to 29.4) | 3.27 (2.16 to 4.95) | 3.94 (1.87 to 8.30) | 3.32 (1.01 to 5.79) | 2.20 (1.57 to 3.07) | 3.87 (1.75 to 8.58) |
|  | Model 3 | 2.97 (1.89 to 4.65) | 4.60 (2.08 to 10.13) | 4.32 (2.43 to 7.69) | 3.12 (2.14 to 4.54) | 6.60 (1.45 to 30.1) | 3.34 (2.20 to 5.06) | 4.55 (2.07 to 10.04) | 3.32 (1.90 to 5.80) | 2.16 (1.54 to 3.03) | 3.94 (1.77 to 8.75) |
| Results are presented as odds ratio (95% confidence interval)  a LiLACS NZ contained two cohorts: Māori and non-Māori population.  b All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) or red blood cell folate<317 nmol/L (LiLACS NZ)and <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation; high CRP was >5 mg/L. Conversion factors: to convert serum vitamin B12 to picograms per milliliter, divide by 0.7378; to convert folate to nanograms per milliliter, divide by 2.265.  c Crude model. Results were presented as odds ratio with a 95% confidence interval.  d Adjusted for age (except Leiden 85-plus Study having all participants aged 85 years old), sex, institutionalisation (except TOOTH which served as an exclusion criteria) and smoking.  e Fully adjusted model: adjusted for age, sex, institutionalisation, smoking, and ≥2 multi-morbidity. Multi-morbidity was composed of stroke, coronary heart disease (CHD), cancer and diabetes. It was stratified into 0 to 1 or 2 and above as a binary variable. Leiden 85-plus Study: sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke, coronary heart disease (CHD) excluding stroke, cancer, diabetes]; LiLACS NZ: age, sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke (cerebrovascular accident (CVA), cardiovascular disease (CVD) excluding stroke, cancer, diabetes]; Newcastle 85+ study: age, sex, institutionalisation, smoking, ≥2 multi-morbidity (CVA, combined cardiac disease excluding CVA, cancer, diabetes); TOOTH: age, sex, smoking, ≥2 multi-morbidity (stroke , coronary heart disease (CHD), cancer, diabetes). | | | | | | | | | | | |

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| **Supplementary Table 10** Meta-Analyses: Iron Deficiency (using two Cut-offs for ferritin concentration) a, Combination of Determinants of Anaemia at Baseline in Association with Presence of Anaemia | | | | | | | | | |
|  |  | Serum Ferritin <15 μg/L (women), <20 μg/L (men) | | | | Serum Ferritin <50 μg/L | | | |
|  |  | N event/N total | N event/N total | OR | Weight | N event/N total | N event/N total | OR | Weight |
|  |  | (anaemia)c | (no anaemia)d | (95% CI) | % | (anaemia)c | (no anaemia)d | (95% CI) | % |
| **Iron Deficiency** | |  |  |  |  |  |  |  |  |
|  | Leiden 85-plus Study | 22/158 | 19/396 | 2.99 (1.51 to 5.89) | 23.4 | 68/158 | 122/396 | 2.12 (1.40 to 3.20) | 26.2 |
|  | LiLACS NZ (Māori) | 1/36 | 4/129 | 0.87 (0.08 to 9.02) | 2.7 | 6/36 | 24/129 | 1.12 (0.40 to 3.15) | 4.1 |
|  | LilACS NZ (Non-Māori) | 6/65 | 14/233 | 1.59 (0.56 to 4.52) | 11.9 | 14/65 | 53/233 | 1.03 (0.51 to 2.06) | 9.2 |
|  | Newcastle 85+ study | 44/224 | 33/527 | 4.19 (2.54 to 6.91) | 34.9 | 107/224 | 207/527 | 1.63 (1.16 to 2.30) | 38.2 |
|  | TOOTH | 35/166 | 21/178 | 2.15 (1.16 to 3.97) | 27.0 | 85/166 | 77/178 | 1.57 (1.01 to 2.46) | 22.3 |
| **Total (*I2*= 24%)** | |  |  | **2.76 (1.87 to 4.07)** | 100.0 | **(*I2*= 0%)** |  | **1.64 (1.32 to 2.02)** | 100.0 |
| **Increase per Additional Abnormal Determinantb** | | | |  |  |  |  |  |  |
|  | Leiden 85-plus Study | 36,64,45,12,1,0/158 | 190,144,58,4,1,0/397 | 2.06 (1.62 to 2.63) | 27.6 | 24,56,53,22,3,0/158 | 132,169,82,10,4,0/397 | 2.05 (1.63 to 2.57) | 26.7 |
|  | LiLACS NZ (Māori) | 8,16,12,9,0,0/45 | 63,69,24,6,0,0/162 | 2.36 (1.55 to 3.59) | 9.1 | 7,15,12,11,0,0/45 | 54,69,31,8,0,0/162 | 2.38 (1.56 to 3.63) | 7.8 |
|  | LilACS NZ (Non-Māori) | 15,23,34,3,0,0/75 | 106,127,42,6,1,0/282 | 1.95 (1.41 to 2.70) | 15.1 | 13,24,30,8,0,0/75 | 91,125,54,9,2,1/282 | 1.75 (1.30 to 2.36) | 15.5 |
|  | Newcastle 85+ study | 41,103,58,21,1,0/224 | 221,223,74,9,1,0/528 | 2.10 (1.72 to 2.58) | 38.6 | 19,98,75,27,5,0/224 | 142,226,134,22,4,0/528 | 1.86 (1.53 to 2.25) | 37.4 |
|  | TOOTH | 95,58,12,2,0,0/167 | 134,42,2,0,0,0/178 | 2.17 (1.44 to 3.27) | 9.6 | 63,74,27,2,1,0/167 | 85,84,9,0,0,0/178 | 1.72 (1.23 to 2.39) | 12.6 |
| **Total (*I2*= 0%)** | |  |  | **2.10 (1.85 to 2.38)** | 100.0 | **(*I2*= 0%)** |  | **1.91 (1.70 to 2.14)** | 100.0 |
| **≥2 Combination of Determinantsb** | | |  |  |  |  |  |  |  |
|  | Leiden 85-plus Study | 58/158 | 63/397 | 2.97 (1.89 to 4.65) | 29.1 | 78/158 | 96/397 | 3.34 (2.20 to 5.07) | 27.1 |
|  | LiLACS NZ (Māori) | 9/45 | 3/162 | 4.60 (2.09 to 10.12) | 9.4 | 23/45 | 39/162 | 4.55 (2.07 to 10.03) | 10.2 |
|  | LilACS NZ (Non-Māori) | 10/75 | 8/282 | 4.32 (2.43 to 7.69) | 17.6 | 38/75 | 66/282 | 3.32 (1.90 to 5.80) | 17.9 |
|  | Newcastle 85+ study | 80/224 | 84/528 | 3.12 (2.14 to 4.54) | 41.4 | 107/224 | 160/528 | 2.16 (1.54 to 3.02) | 34.9 |
|  | TOOTH | 14/167 | 2/178 | 6.60 (1.45 to 30.03) | 2.6 | 30/167 | 9/178 | 3.94 (1.77 to 8.74) | 10.0 |
| **Total (*I2*= 0%)** | |  |  | **3.44 (2.70 to 4.38)** | 100.0 | **(*I2*= 26%)** |  | **3.00 (2.29 to 3.94)** | 100.0 |
| Abbreviations: OR, odds ratio; CI, confidence interval.  a Results of fully adjusted model (model 3): adjusted for age, sex, institutionalisation, smoking and ≥2 multi-morbidity.  b All four studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP.  c Population with determinant within total anemic population.  d Population with determinant within total non-anemic population. | | | | | | | | | |

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| **Supplementary Table 11** Prospective results: the association between iron deficiency, using two cut-offs for ferritin concentration, and the onset of anaemia at baseline in three studies | | | | | | | |
|  |  | Serum Ferritin <15 μg/L (women), <20 μg/L (men) | | | Serum Ferritin <50 μg/L | | |
|  |  | Leiden 85-plus Study (N=361) | Newcastle 85+ study (N=418) | TOOTH  (N=97) | Leiden 85-plus Study (N=361) | Newcastle 85+ study (N=418) | TOOTH  (N=97) |
|  |  | HR (95%CI) | HR (95%CI) | HR (95%CI) | HR (95%CI) | HR (95%CI) | HR (95%CI) |
| Iron Deficiency | |  |  |  |  |  |  |
|  | Model 1b | 1.45 (0.63 to 3.31) | 2.38 (1.34 to 4.26) | 0.89 (0.31 to 2.54) | 1.11 (0.73 to 1.70) | 1.62 (1.11 to 2.36) | 0.85 (0.42 to 1.71) |
|  | Model 2c | 1.47 (0.64 to 3.36) | 2.40 (1.34 to 4.30) | 0.88 (0.31 to 2.53) | 1.31 (0.85 to 2.01) | 1.82 (1.23 to 2.71) | 0.92 (0.44 to 1.91) |
|  | Model 3d | 1.48 (0.64 to 3.40) | 2.41 (1.35 to 4.32) | 0.88 (0.30 to 2.53) | 1.31 (0.85 to 2.01) | 1.80 (1.21 to 2.67) | 0.92 (0.44 to 1.91) |
| Increase per Additional Abnormal Determinanta | | | |  |  |  |  |
|  | Model 1c | 1.34 (1.07 to 1.69) | 1.58 (1.26 to 1.97) | 1.38 (0.71 to 2.70) | 1.29 (1.04 to 1.59) | 1.52 (1.25 to 1.86) | 1.16 (0.65 to 2.08) |
| Model 2 | 1.35 (1.06 to 1.73) | 1.57 (1.25 to 1.98) | 1.28 (0.65 to 2.53) | 1.34 (1.08 to 1.67) | 1.56 (1.27 to 1.92) | 1.17 (0.66 to 2.10) |
| Model 3 | 1.35 (1.06 to 1.73) | 1.58 (1.25 to 1.98) | 1.28 (0.65 to 2.53) | 1.34 (1.08 to 1.67) | 1.55 (1.27 to 1.91) | 1.17 (0.66 to 2.10) |
| ≥2 Combination of Determinants | | |  |  |  |  |  |
|  | Model 1 | 1.74 (1.07 to 2.85) | 1.99 (1.29 to 3.07) | 3.00 (0.41 to 22.0) | 1.76 (1.11 to 2.71) | 1.83 (1.25 to 2.68) | 1.50 (0.36 to 6.27) |
|  | Model 2 | 1.86 (1.12 to 3.11) | 2.01 (1.30 to 3.12) | 1.97 (0.25 to 15.4) | 1.92 (1.23 to 2.99) | 1.90 (1.29 to 2.80) | 1.40 (0.33 to 5.89) |
|  | Model 3 | 1.87 (1.12 to 3.12) | 2.02 (1.30 to 3.13) | 1.98 (0.25 to 15.5) | 1.94 (1.25 to 3.01) | 1.89 (1.28 to 2.78) | 1.40 (0.33 to 5.94) |
| Abbreviations: HR, hazard ratio; CI, confidence interval.  a All three studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7 nmol/L (Leiden 85-plus Study and TOOTH) and <340 nmol/L (Newcastle 85+ study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation; high CRP was >5 mg/L.  b Crude model. Results were presented as hazard ratio with a 95% confidence interval.  c Adjusted for age (except Leiden 85-plus Study having all participants aged 85 years old), sex, institutionalisation (except TOOTH which served as an exclusion criteria) and smoking.  d Fully adjusted model: adjusted for age, sex, institutionalisation, smoking, and ≥2 multi-morbidity. Multi-morbidity was composed of stroke, coronary heart disease (CHD), cancer and diabetes. It was stratified into 0 to 1 or 2 and above as a binary variable. Leiden 85-plus Study: sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke, coronary heart disease (CHD) excluding stroke, cancer, diabetes]; Newcastle 85+ study: age, sex, institutionalisation, smoking, ≥2 multi-morbidity (CVA, combined cardiac disease excluding CVA, cancer, diabetes); TOOTH: age, sex, smoking, ≥2 multi-morbidity (stroke, coronary heart disease (CHD), cancer, diabetes). | | | | | | | |

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| **Supplementary Table 12**. Meta-Analyses: Iron Deficiency (using two Cut-offs for ferritin concentration)and Combination of Determinants of Anaemia in Association with Onset of Anaemia in Three Studiesabc | | | | | | | | | |
|  |  | Serum Ferritin <15 μg/L (women), <20 μg/L (men) | | | | Serum Ferritin <50 μg/L | | | |
|  |  | N event/N total | N event/N total | HR | Weight | N event/N total | N event/N total | HR | Weight |
|  |  | (anaemia)d | (no anaemia)e | (95% CI) | % | (anaemia)d | (no anaemia)e | (95% CI) | % |
| **Iron Deficiency** | |  |  |  |  |  |  |  |  |
|  | Leiden 85-plus Study | 6/98 | 11/262 | 1.48 (0.64 to 3.40) | 30.8 | 32/98 | 81/262 | 1.31 (0.85 to 2.02) | 39.1 |
|  | Newcastle 85+ study | 13/109 | 12/309 | 2.41 (1.35 to 4.32) | 47.6 | 57/109 | 114/309 | 1.79 (1.21 to 2.67) | 43.3 |
|  | TOOTH | 4/33 | 9/64 | 0.88 (0.30 to 2.53) | 21.6 | 13/33 | 29/64 | 0.92 (0.44 to 1.91) | 17.6 |
| **Total (*I2*= 32%)** | |  |  | **1.67 (0.96 to 2.90)** | 100.0 | **(*I2*= 29%)** |  | **1.41 (1.01** to **1.97)** | 100.0 |
| **Increase per Additional Abnormal Determinantc** | | |  |  |  |  |  |  |  |
|  | Leiden 85-plus Study | 41,37,18,2,0,0/98 | 139,91,30,2,1,0/263 | 1.35 (1.06 to 1.73) | 44.0 | 30,38,25,3,2,0/98 | 96,112,48,5,2,0/263 | 1.34 (1.08 to 1.67) | 43.9 |
|  | Newcastle 85+ study | 30,52,23,4,0,0/109 | 149,124,32,4,0,0/309 | 1.58 (1.25 to 1.98) | 50.3 | 14,49,35,9,2,0/109 | 97,134,67,10,1,0/309 | 1.55 (1.27 to 1.91) | 49.9 |
|  | TOOTH | 23,9,1,0,0,0/33 | 50,14,0,0,0,0/64 | 1.28 (0.65 to 2.53) | 5.7 | 15,16,2,0,0,0/33 | 32,30,2,0,0,0/64 | 1.17 (0.66 to 2.10) | 6.2 |
| **Total (*I2*= 0%)** | |  |  | **1.46 (1.24** to **1.71)** | 100.0 | **(*I2*= 0%)** |  | **1.43 (1.24** to **1.66)** | 100.0 |
| **≥2 Combination of Determinantsc** | | |  |  |  |  |  |  |  |
|  | Leiden 85-plus Study | 20/98 | 33/263 | 1.87 (1.12 to 3.12) | 41.1 | 30/98 | 55/263 | 1.93 (1.24 to 3.00) | 41.7 |
|  | Newcastle 85+ study | 27/109 | 36/309 | 2.02 (1.30 to 3.13) | 56.3 | 46/109 | 78/309 | 1.89 (1.28 to 2.78) | 54.4 |
|  | TOOTH | 1/33 | 0/64 | 1.98 (0.25 to 15.53) | 2.6 | 2/33 | 2/64 | 1.40 (0.33 to 5.94) | 3.9 |
| **Total (*I2*= 0%)** | |  |  | **1.95 (1.40** to **2.71)** | 100.0 | **(*I2*= 0%)** |  | **1.88 (1.41** to **2.50)** | 100.0 |
| Abbreviations: HR, hazard ratio; CI, confidence interval.  a Iron deficiency was defined as ferritin <20 μg/L for men, <15 μg/L for women; vitamin B12 deficiency was <150 pmol/L; folate deficiency was serum folate level <7nmol/L (Leiden 85-plus Study and TOOTH) or <340 nmol/L (Newcastle 85+ Study); low eGFR was <45 mL/min/1.73 m2, eGFR was calculated using MDRD (Modification of Diet in Renal Disease) Study equation from the National Kidney Foundation; high CRP was >5 mg/L.  b Results of fully adjusted model (model 3): adjusted for age, sex, institutionalisation, smoking and ≥2 multi-morbidity. Multi-morbidity was composed of stroke, coronary heart disease (CHD), cancer and diabetes. It was stratified into 0 to 1 or 2 and above as a binary variable. Leiden 85-plus Study: sex, institutionalisation, smoking and ≥2 multi-morbidity [stroke, coronary heart disease (CHD) excluding stroke, cancer, diabetes]; Newcastle 85+ study: age, sex, institutionalisation, smoking, ≥2 multi-morbidity (CVA, combined cardiac disease excluding CVA, cancer, diabetes); TOOTH: age, sex, smoking, ≥2 multi-morbidity (stroke, coronary heart disease (CHD), cancer, diabetes).  c LiLACS NZ did not have follow-up data for hemoglobin; TOOTH: since not all determinants were collected at baseline, 3-year follow-up was defined as baseline, and 6-year follow-up as follow-up data. All three studies included five determinants: iron, vitamin B12, folate deficiency, low eGFR, and high CRP.  d Population with determinant within total anemic population during follow-up.  e Population with determinant within total non-anemic population during follow-up. | | | | | | | | | |