S**pplementary Table 1**: Read codes to identify each type of dementia diagnosis

|  |  |  |
| --- | --- | --- |
| Read code | Read term | N (% of all dementia) |
| **Alzheimer’s disease/Unspecified dementia** | | 49161 (75.0%) |
| e00..12 | Senile/presenile dementia | 12116 (18.5%) |
| f110.00 | Alzheimer's disease | 10194 (15.6%) |
| eu02z00 | [X] Unspecified dementia | 8206 (12.5%) |
| e00..11 | Senile dementia | 4179 (6.4%) |
| eu00.00 | [X]Dementia in Alzheimer's disease | 4105 (6.3%) |
| eu02z14 | [X] Senile dementia NOS | 2720 (4.2%) |
| e000.00 | Uncomplicated senile dementia | 2086 (3.2%) |
| eu00z11 | [X]Alzheimer's dementia unspec | 1871 (2.9%) |
| 1461.00 | H/O: dementia | 1821 (2.8%) |
| eu00z00 | [X]Dementia in Alzheimer's disease, unspecified | 246 (0.4%) |
| eu00112 | [X]Senile dementia,Alzheimer's type | 243 (0.4%) |
| eu00100 | [X]Dementia in Alzheimer's disease with late onset | 193 (0.3%) |
| e001.00 | Presenile dementia | 192 (0.3%) |
| f110100 | Alzheimer's disease with late onset | 159 (0.2%) |
| f110000 | Alzheimer's disease with early onset | 146 (0.2%) |
| e002100 | Senile dementia with depression | 119 (0.2%) |
| e002000 | Senile dementia with paranoia | 108 (0.2%) |
| eu00000 | [X]Dementia in Alzheimer's disease with early onset | 74 (0.1%) |
| e003.00 | Senile dementia with delirium | 59 (0.1%) |
| e001z00 | Presenile dementia NOS | 55 (0.1%) |
| eu02z16 | [X] Senile dementia, depressed or paranoid type | 44 (0.1%) |
| e002.00 | Senile dementia with depressive or paranoid features | 44 (0.1%) |
| e001200 | Presenile dementia with paranoia | 38 (0.1%) |
| e001300 | Presenile dementia with depression | 24 (<0.1%) |
| eu02z13 | [X] Primary degenerative dementia NOS | 23 (<0.1%) |
| eu04100 | [X]Delirium superimposed on dementia | 18 (<0.1%) |
| eu00011 | [X]Presenile dementia,Alzheimer's type | 12 (<0.1%) |
| eu00113 | [X]Primary degen dementia of Alzheimer's type, senile onset | 12 (<0.1%) |
| e001100 | Presenile dementia with delirium | 11 (<0.1%) |
| eu02z11 | [X] Presenile dementia NOS | 11 (<0.1%) |
| e001000 | Uncomplicated presenile dementia | 10 (<0.1%) |
| eu00111 | [X]Alzheimer's disease type 1 | 8 (<0.1%) |
| e002z00 | Senile dementia with depressive or paranoid features NOS | 6 (<0.1%) |
| eu00012 | [X]Primary degen dementia, Alzheimer's type, presenile onset | 6 (<0.1%) |
| fyu3000 | [X]Other Alzheimer's disease | 1 (<0.1%) |
| eu00013 | [X]Alzheimer's disease type 2 | 1 (<0.1%) |
| **Vascular dementia** | | 13816 (21.1%) |
| eu01.00 | [X]Vascular dementia | 11196 (17.1%) |
| e004.11 | Multi infarct dementia | 915 (1.4%) |
| e004.00 | Arteriosclerotic dementia | 435 (0.7%) |
| eu01100 | [X]Multi-infarct dementia | 274 (0.4%) |
| eu01.11 | [X]Arteriosclerotic dementia | 245 (0.4%) |
| eu01z00 | [X]Vascular dementia, unspecified | 245 (0.4%) |
| eu01300 | [X]Mixed cortical and subcortical vascular dementia | 202 (0.3%) |
| e004z00 | Arteriosclerotic dementia NOS | 119 (0.2%) |
| eu01y00 | [X]Other vascular dementia | 66 (0.1%) |
| eu01200 | [X]Subcortical vascular dementia | 56 (0.1%) |
| eu01000 | [X]Vascular dementia of acute onset | 18 (<0.1%) |
| e004000 | Uncomplicated arteriosclerotic dementia | 17 (<0.1%) |
| e004300 | Arteriosclerotic dementia with depression | 14 (<0.1%) |
| e004200 | Arteriosclerotic dementia with paranoia | 9 (<0.1%) |
| eu01111 | [X]Predominantly cortical dementia | 5 (<0.1%) |
| **Other** | | 2541 (3.9%) |
| eu02500 | [X]Lewy body dementia | 528 (0.8%) |
| eu02300 | [X]Dementia in Parkinson's disease | 412 (0.6%) |
| eu00200 | [X]Dementia in Alzheimer's dis, atypical or mixed type | 400 (0.6%) |
| e041.00 | Dementia in conditions EC | 376 (0.6%) |
| f116.00 | Lewy body disease | 335 (0.5%) |
| eu02.00 | [X]Dementia in other diseases classified elsewhere | 190 (0.3%) |
| e012.11 | Alcoholic dementia NOS | 113 (0.2%) |
| eu10711 | [X]Alcoholic dementia NOS | 76 (0.1%) |
| f111.00 | Pick's disease | 31 (<0.1%) |
| eu02200 | [X]Dementia in Huntington's disease | 19 (<0.1%) |
| eu02y00 | [X]Dementia in other specified diseases classif elsewhere | 15 (<0.1%) |
| e012.00 | Other alcoholic dementia | 14 (<0.1%) |
| eu02000 | [X]Dementia in Pick's disease | 13 (<0.1%) |
| eu02100 | [X]Dementia in Creutzfeldt-Jakob disease | 12 (<0.1%) |
| e004100 | Arteriosclerotic dementia with delirium | 4 (<0.1%) |
| e02y100 | Drug-induced dementia | 2 (<0.1%) |
| eu02400 | [X]Dementia in human immunodef virus [HIV] disease | 1 (<0.1%) |

**Supplementary table 2**:Age and sex adjusted rate ratios per 10mmHg higher long-term average **diastolic BP** for dementia, Alzheimer’s disease and vascular dementia stratified by age-at-risk and time since baseline blood pressure measurement

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age at risk | 0-5 years | |  | 5-10 years | | |  | | 10+ years | | |
|  |  | Events | Rate ratio (95% CI) |  | Events | Rate ratio (95% CI) |  | | Events | | Rate ratio (95% CI) |
| All dementia |  |  |  |  |  |  |  | |  | |  |
|  | <70 | 2245 | 0.757 (0.689 to 0.831) |  | 1762 | 0.807 (0.727 to 0.895) |  | | 1450 | | 1.095 (0.980 to 1.224) |
|  | 70-84 | 13674 | 0.807 (0.778 to 0.838) |  | 12445 | 0.875 (0.841 to 0.910) |  | | 12125 | | 0.951 (0.913 to 0.990) |
|  | 85+ | 7651 | 0.818 (0.780 to 0.858) |  | 6602 | 0.877 (0.832 to 0.925) |  | | 7564 | | 0.910 (0.865 to 0.958) |
|  | Overall | 23570 | 0.806 (0.784 to 0.829) |  | 20809 | 0.871 (0.845 to 0.898) |  | | 21139 | | 0.948 (0.919 to 0.977) |
| Alzheimer's disease | |  |  |  |  |  |  | |  | |  |
|  | <70 | 1703 | 0.725 (0.651 to 0.807) |  | 1308 | 0.768 (0.680 to 0.868) |  | | 996 | | 0.984 (0.859 to 1.127) |
|  | 70-84 | 10785 | 0.797 (0.765 to 0.831) |  | 9035 | 0.878 (0.838 to 0.919) |  | | 8497 | | 0.912 (0.869 to 0.957) |
|  | 85+ | 6310 | 0.804 (0.763 to 0.847) |  | 5037 | 0.843 (0.793 to 0.896) |  | | 5490 | | 0.877 (0.826 to 0.931) |
|  | Overall | 18798 | 0.792 (0.768 to 0.817) |  | 15380 | 0.858 (0.828 to 0.889) |  | | 14983 | | 0.905 (0.873 to 0.938) |
| Vascular dementia | |  |  |  |  |  |  | |  | |  |
|  | <70 | 348 | 1.033 (0.819 to 1.303) |  | 301 | 0.983 (0.767 to 1.259) |  | | 314 | | 1.425 (1.131 to 1.796) |
|  | 70-84 | 2492 | 0.876 (0.803 to 0.955) |  | 2872 | 0.896 (0.825 to 0.972) |  | | 3015 | | 1.061 (0.979 to 1.149) |
|  | 85+ | 1210 | 0.911 (0.807 to 1.027) |  | 1415 | 1.014 (0.905 to 1.137) |  | | 1849 | | 1.001 (0.904 to 1.109) |
|  | Overall | 4050 | 0.895 (0.837 to 0.958) |  | 4588 | 0.937 (0.878 to 0.999) |  | | 5178 | | 1.061 (0.998 to 1.127) |

**Supplementary Table 3:**  Rate ratios of systolic blood pressure with dementia with varying degrees of statistical adjustment in 2,324,605 patients with complete covariate information

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Rate ratio (95% CI) | | |
|  | Period of follow up | Age at risk | Events | Age and sex adjusted | Age sex and BMI adjusted | Adjusted for 10 additional covariates\* |
| **All dementia** | |  |  |  |  |  |
|  | 0-5 | <70 | 1931 | 0.857 (0.812 to 0.905) | 0.902 (0.854 to 0.953) | 0.903 (0.855 to 0.954) |
|  |  | 70-84 | 10602 | 0.849 (0.831 to 0.868) | 0.870 (0.851 to 0.889) | 0.882 (0.863 to 0.902) |
|  |  | 85+ | 4676 | 0.838 (0.812 to 0.865) | 0.847 (0.821 to 0.875) | 0.855 (0.828 to 0.883) |
|  |  | Overall | 17209 | 0.847 (0.832 to 0.861) | 0.866 (0.852 to 0.881) | 0.878 (0.863 to 0.893) |
|  | 5-10 | <70 | 1663 | 0.949 (0.895 to 1.005) | 0.974 (0.919 to 1.033) | 0.969 (0.913 to 1.028) |
|  |  | 70-84 | 11300 | 0.948 (0.928 to 0.968) | 0.963 (0.944 to 0.984) | 0.971 (0.951 to 0.992) |
|  |  | 85+ | 5304 | 0.927 (0.900 to 0.955) | 0.935 (0.908 to 0.963) | 0.942 (0.914 to 0.971) |
|  |  | Overall | 18267 | 0.942 (0.927 to 0.958) | 0.956 (0.941 to 0.972) | 0.964 (0.948 to 0.980) |
|  | 10+ | <70 | 1419 | 1.059 (0.995 to 1.127) | 1.064 (0.998 to 1.135) | 1.037 (0.972 to 1.106) |
|  |  | 70-84 | 11701 | 0.993 (0.973 to 1.013) | 0.999 (0.979 to 1.020) | 0.997 (0.976 to 1.018) |
|  |  | 85+ | 6932 | 0.955 (0.930 to 0.980) | 0.962 (0.937 to 0.987) | 0.965 (0.939 to 0.990) |
|  |  | Overall | 20052 | 0.984 (0.969 to 0.999) | 0.991 (0.975 to 1.006) | 0.991 (0.975 to 1.007) |
| **Alzheimer’s disease** | |  |  |  |  |  |
|  | 0-5 | <70 | 1449 | 0.857 (0.805 to 0.912) | 0.909 (0.854 to 0.968) | 0.909 (0.853 to 0.968) |
|  |  | 70-84 | 8216 | 0.845 (0.824 to 0.866) | 0.867 (0.846 to 0.889) | 0.873 (0.852 to 0.896) |
|  |  | 85+ | 3738 | 0.829 (0.799 to 0.859) | 0.839 (0.809 to 0.869) | 0.843 (0.813 to 0.874) |
|  |  | Overall | 13403 | 0.841 (0.825 to 0.857) | 0.862 (0.845 to 0.879) | 0.868 (0.851 to 0.885) |
|  | 5-10 | <70 | 1231 | 0.906 (0.847 to 0.970) | 0.932 (0.869 to 0.998) | 0.936 (0.873 to 1.003) |
|  |  | 70-84 | 8157 | 0.951 (0.928 to 0.974) | 0.970 (0.946 to 0.994) | 0.973 (0.949 to 0.997) |
|  |  | 85+ | 3976 | 0.918 (0.887 to 0.950) | 0.927 (0.895 to 0.959) | 0.929 (0.897 to 0.961) |
|  |  | Overall | 13364 | 0.938 (0.920 to 0.956) | 0.954 (0.936 to 0.973) | 0.957 (0.939 to 0.976) |
|  | 10+ | <70 | 972 | 0.975 (0.902 to 1.053) | 0.971 (0.896 to 1.051) | 0.951 (0.877 to 1.030) |
|  |  | 70-84 | 8198 | 0.963 (0.939 to 0.986) | 0.973 (0.949 to 0.997) | 0.972 (0.948 to 0.997) |
|  |  | 85+ | 5001 | 0.941 (0.912 to 0.970) | 0.950 (0.921 to 0.980) | 0.952 (0.923 to 0.982) |
|  |  | Overall | 14171 | 0.956 (0.938 to 0.974) | 0.966 (0.948 to 0.984) | 0.967 (0.949 to 0.985) |
| **Vascular dementia** | |  |  |  |  |  |
|  | 0-5 | <70 | 314 | 0.963 (0.844 to 1.100) | 0.968 (0.847 to 1.106) | 0.976 (0.855 to 1.114) |
|  |  | 70-84 | 2065 | 0.891 (0.847 to 0.937) | 0.907 (0.863 to 0.954) | 0.967 (0.936 to 0.999) |
|  |  | 85+ | 853 | 0.878 (0.814 to 0.948) | 0.884 (0.819 to 0.953) | 0.967 (0.921 to 1.014) |
|  |  | Overall | 3232 | 0.892 (0.857 to 0.929) | 0.906 (0.870 to 0.942) | 0.975 (0.950 to 1.001) |
|  | 5-10 | <70 | 289 | 1.165 (1.023 to 1.327) | 1.166 (1.022 to 1.330) | 1.120 (0.982 to 1.279) |
|  |  | 70-84 | 2646 | 0.972 (0.931 to 1.015) | 0.978 (0.937 to 1.021) | 1.003 (0.960 to 1.047) |
|  |  | 85+ | 1214 | 0.970 (0.912 to 1.033) | 0.975 (0.916 to 1.037) | 1.001 (0.940 to 1.065) |
|  |  | Overall | 4149 | 0.983 (0.950 to 1.018) | 0.988 (0.955 to 1.023) | 1.012 (0.978 to 1.048) |
|  | 10+ | <70 | 311 | 1.273 (1.123 to 1.444) | 1.295 (1.139 to 1.472) | 1.235 (1.086 to 1.404) |
|  |  | 70-84 | 2917 | 1.095 (1.052 to 1.140) | 1.092 (1.048 to 1.137) | 1.087 (1.044 to 1.132) |
|  |  | 85+ | 1722 | 1.002 (0.951 to 1.056) | 1.003 (0.952 to 1.057) | 1.009 (0.957 to 1.064) |
|  |  | Overall | 4950 | 1.071 (1.038 to 1.104) | 1.070 (1.037 to 1.103) | 1.069 (1.037 to 1.103) |

\*Adjusted for age, sex, body mass index, alcohol consumption, socio-economic status (fifths of practice-level Townsend score), or a history of any of the following: anti-hypertensive or statin use within previous year, stroke, atrial fibrillation, diabetes, heart failure, chronic obstructive pulmonary disease, and diabetes.

**Supplementary Table 4:** Rate ratios of per 10mmHg higher long-term average systolic blood pressure with dementia by age-at-risk and time since index measurement **during long-term follow up (>10 years post measurement)**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age at risk | 10-12.5 years | |  | 12.5-15 years | |  | 15+ years | | All follow up >10 years | |
|  |  | Events | Rate ratio (95% CI) |  | Events | Rate ratio (95% CI) |  | Events | Rate ratio (95% CI) | Events | Rate ratio (95% CI) |
| All dementia | |  |  |  |  |  |  |  |  |  |  |
|  | <70 | 627 | 1.070 (0.975 to 1.174) |  | 394 | 1.054 (0.936 to 1.186) |  | 429 | 1.093 (0.973 to 1.228) | 1450 | 1.067 (1.003 to 1.134) |
|  | 70-84 | 4901 | 0.994 (0.963 to 1.026) |  | 3331 | 0.992 (0.955 to 1.031) |  | 3893 | 1.016 (0.980 to 1.053) | 12125 | 0.995 (0.975 to 1.015) |
|  | 85+ | 2980 | 0.953 (0.916 to 0.991) |  | 2039 | 0.945 (0.901 to 0.992) |  | 2545 | 0.980 (0.939 to 1.023) | 7564 | 0.955 (0.931 to 0.979) |
|  | Overall | 8508 | 0.984 (0.961 to 1.008) |  | 5764 | 0.980 (0.952 to 1.009) |  | 6867 | 1.006 (0.979 to 1.033) | 21139 | 0.984 (0.970 to 0.999) |
| Alzheimer's disease | |  |  |  |  |  |  |  |  |  |  |
|  | <70 | 430 | 0.972 (0.866 to 1.090) |  | 265 | 0.931 (0.801 to 1.081) |  | 301 | 1.061 (0.922 to 1.221) | 996 | 0.981 (0.909 to 1.058) |
|  | 70-84 | 3502 | 0.962 (0.926 to 0.999) |  | 2319 | 0.951 (0.908 to 0.996) |  | 2676 | 0.989 (0.946 to 1.033) | 8497 | 0.965 (0.942 to 0.988) |
|  | 85+ | 2199 | 0.951 (0.908 to 0.996) |  | 1509 | 0.918 (0.868 to 0.972) |  | 1782 | 0.956 (0.909 to 1.007) | 5490 | 0.942 (0.914 to 0.970) |
|  | Overall | 6131 | 0.959 (0.932 to 0.986) |  | 4093 | 0.939 (0.907 to 0.973) |  | 4759 | 0.979 (0.947 to 1.011) | 14983 | 0.957 (0.940 to 0.975) |
| Vascluar dementia | |  |  |  |  |  |  |  |  |  |  |
|  | <70 | 133 | 1.298 (1.075 to 1.569) |  | 97 | 1.301 (1.042 to 1.625) |  | 84 | 1.193 (0.925 to 1.539) | 314 | 1.269 (1.120 to 1.438) |
|  | 70-84 | 1175 | 1.103 (1.036 to 1.174) |  | 836 | 1.121 (1.041 to 1.208) |  | 1004 | 1.101 (1.027 to 1.180) | 3015 | 1.095 (1.052 to 1.139) |
|  | 85+ | 712 | 0.969 (0.893 to 1.051) |  | 466 | 1.038 (0.940 to 1.146) |  | 671 | 1.053 (0.970 to 1.144) | 1849 | 1.005 (0.956 to 1.057) |
|  | Overall | 2020 | 1.064 (1.014 to 1.116) |  | 1399 | 1.103 (1.041 to 1.168) |  | 1759 | 1.086 (1.031 to 1.144) | 5178 | 1.070 (1.038 to 1.102) |

**Supplementary Table 5:** Age and sex adjusted risk ratios for **death and stroke** per 10mmHg higher long-term average systolic blood pressure stratified by age-at-risk and time since baseline systolic blood pressure measurement

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age at risk | 0-5 years | | |  | | 5-10 years | | | |  | | 10+ years | | | |
|  |  | Events | Rate ratio (95% CI) | |  | | Events | | Rate ratio (95% CI) | |  | | Events | | Rate ratio (95% CI) | |
| **Incidence of stroke** | | | |  | |  | |  | |  | |  | |  | |
|  | <70 | 21526 | 1.376 (1.356 to 1.396) | |  | | 13434 | | 1.299 (1.274 to 1.324) | |  | | 8374 | | 1.281 (1.249 to 1.313) | |
|  | 70-84 | 28052 | 1.101 (1.088 to 1.115) | |  | | 19062 | | 1.090 (1.073 to 1.107) | |  | | 15612 | | 1.110 (1.091 to 1.130) | |
|  | 85+ | 9115 | 0.984 (0.963 to 1.005) | |  | | 6652 | | 1.027 (1.001 to 1.054) | |  | | 6500 | | 1.062 (1.035 to 1.090) | |
|  | Overall | 58693 | 1.169 (1.159 to 1.179) | |  | | 39148 | | 1.144 (1.132 to 1.157) | |  | | 30486 | | 1.145 (1.131 to 1.159) | |
| **All-cause death** | |  |  | |  | |  | |  | |  | |  | |  | |
|  | <70 | 52290 | 1.041 (1.030 to 1.051) | |  | | 32164 | | 1.188 (1.173 to 1.203) | |  | | 19291 | | 1.264 (1.244 to 1.285) | |
|  | 70-84 | 93248 | 0.859 (0.853 to 0.865) | |  | | 66513 | | 1.040 (1.031 to 1.048) | |  | | 50494 | | 1.142 (1.131 to 1.153) | |
|  | 85+ | 53711 | 0.775 (0.767 to 0.782) | |  | | 38468 | | 0.978 (0.967 to 0.988) | |  | | 36726 | | 1.080 (1.068 to 1.092) | |
|  | Overall | 199249 | 0.870 (0.866 to 0.875) | |  | | 137145 | | 1.051 (1.044 to 1.057) | |  | | 106511 | | 1.139 (1.132 to 1.147) | |

**Supplementary Table 6:** Rate ratios of systolic blood pressure with dementia, Alzheimer’s disease and vascular dementia amongst patients aged <60 or <65, restricted to long term follow-up ( >10 years after post-measurement)

|  |  |  |  |
| --- | --- | --- | --- |
|  | Rate ratio (95% CI) | | |
|  | Any dementia | Alzheimer's disease | Vascular dementia |
| Amongst patients aged <60 | 1.09 (0.91,1.31) | 0.87 (0.69,1.08) | 1.95 (1.40,2.72) |
| Amongst patients aged <65 (including those aged <60) | 1.10 (1.00,1.22) | 1.00 (0.88,1.13) | 1.42 (1.14,1.77) |

**Supplementary Figure 1:** Age and sex standardized rates of dementia by long-term average systolic blood pressure



**Supplementary Figure 2:** Age and sex standardized rates of dementia by long-term average **diastolic blood pressure** during the A) the first 5-years after measurement B) 5-10 years after measurement; C) >10 years after measurement

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**Supplementary Figure 3:** Age and sex standardized rates of **stroke** by long-term average systolic blood pressure during the A) the first 5-years after measurement B) 5-10 years after measurement; C) >10 years after measurement

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**Supplementary Figure 4:** Age and sex standardized rates for **all-cause mortality** by long-term average systolic blood pressure during the A) the first 5-years after measurement B) 5-10 years after measurement; C) >10 years after measurement

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**Supplementary Appendix**

A: Description of use of repeat measurements

Measurement error and within-individual variation in blood pressure means that estimated associations between baseline blood pressure measurements and dementia would be under-estimated if the associations were not adjusted for this variability. In order to correct for this bias, commonly known as regression dilution bias, we used repeat measurements of blood pressure taken within the first 5 years of follow up after the index blood pressure measurement.

We performed a random intercepts regression where repeat blood pressure measurements were the outcome variable, baseline blood pressure was the explanatory variable, and the random intercept was fit for each individual patient. The regression coefficient for baseline blood pressure explains the increase in repeat blood pressure per 1 unit increase in baseline blood pressure and is known as the regression dilution ratio. The inverse of the regression dilution ratio is known as the attenuation factor.

To estimate the effect of a 10mmHg increase in long-term average levels of blood pressure, we therefore estimated the association between baseline blood pressure and dementia and multiplied the regression coefficient by the attenuation factor. To graphically display the risk of dementia according to long-term average blood pressure measurements, we “shrunk” the mean value within each tenth of baseline blood pressure towards the overall mean blood pressure. This was achieved using the following steps. First, the difference between the mean value amongst all patients and the mean value in each tenth is calculated. Second, this difference is multiplied by the regression dilution ratio. Third, the regression dilution adjusted difference (i.e. the value calculated in the second step) is added to the overall mean blood pressure.

**B:** Frailty analyses

*Methods*

It is known that studies which assess disorders strongly associated with increasing age can be prone to bias due to selective mortality, particularly where the exposure is associated with mortality risk. We were concerned that selective mortality could bias the association between blood pressure (BP) and dementia because high BP is associated with increased mortality risk.

Bias can occur when uncontrolled risk factors are associated with both death and dementia, referred to here as “joint frailty” for both conditions. The amount of joint frailty for both conditions is unknown and is not estimable from the data without making additional assumptions. We therefore simulated the results of our study using a range of joint frailties distributions. The aim was to understand the plausible impact of joint frailty on our study findings. The simulation study was conducted as follows:

1. 2,593,629 million simulated individuals were randomly assigned values for systolic BP, *SBPi ,* using a normal distribution with a mean of 140mmHg and a standard deviation of 10mmHg. This mirrors the distribution of long-term average BP that we observed.
2. Each patient entered the simulated dataset at age 40, the minimum age to enter our study; very few deaths occur in the general population before age 40, so any bias caused by interdependence between death and dementia before age 40 will be negligible.
3. Estimated age-specific death rates, λAGE, were estimated for patients in 5 year bands from our CPRD dataset.
4. Individuals were randomly assigned a frailty term, ωi, sampled from a truncated\* gamma distribution. This term represents a patient’s frailty for both death and dementia. We varied the variance of the frailty distribution to represent a range of plausible scenarios.+
5. A rate ratio of 1.264 per 10mmHg increase is applied to each patient’s age-specific death rate, with the hazard ratio (HR) applied around the mean blood pressure of 140mmHg. This is the rate ratio observed in the real CPRD dataset for death in patients aged <70 who had a systolic BP measurement at least 10 years ago, and is the strongest association of systolic BP with death in our CPRD dataset across all age groups (**Supplementary Table 4, Supplementary Figure 4**). A patient’s age specific rate of death is therefore given by: λAGEX ωiX exp(log(1.264)X(140-SBPi))
6. Each individual’s time to death was sampled from an exponential distribution using their age-specific rates of death.
7. Estimated dementia rates, µAGE, were calculated in 5-year age bands from our CPRD dataset. A patient’s age specific rate of dementia is therefore: µAGE X ωi. Therefore, there is no direct relationship between BP and dementia: an unbiased estimate of the HR for blood pressure on dementia should be 1.00.
8. Each individual’s time to dementia was sampled from an exponential distribution according to their age-specific rate of dementia.
9. If time to death is less than time to dementia, the indicator for dementia is set to 0 and follow up is censored at the time to death to replicate the observable data.

\* We used a truncated distribution, truncating at a frailty of 0.2 and 5, because the gamma distribution is highly skew and we wanted to avoid patients with implausibly long times to death.

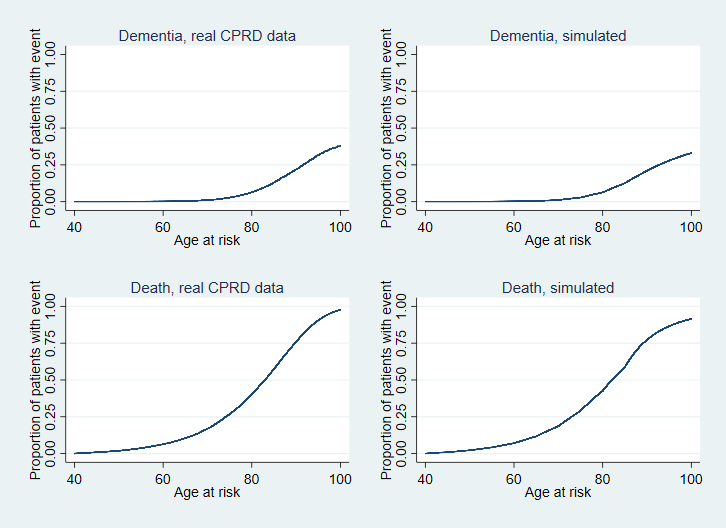
+We varied α from 0.2 to1 in steps of 0.2, and sampled from Ga(1/α,α). For no frailty we set ωi=1 for all patients

*Results*

To ensure that our simulated data had similar properties to the real CPRD dataset, we plotted Kaplan Meier failure curves for each of dementia and death in both the real CPRD data and the simulated data. The **Appendix Figure** shows that the shapes of the Kaplan Meier curves are very similar between CPRD and the simulated data, indicating that the modelled age-specific rates of dementia and death in our simulations are a good approximation of the real CPRD data.

The **Appendix Table** summarises the results of the simulation study. We calculated estimated HRs for dementia per 10mmHg higher SBP in each simulated dataset. To give an intuitive feel of the strength of the frailty that we assumed, we calculated the mean frailty amongst patients by decade of death. Due to the simulation setup, frailty was related multiplicatively to dementia such that a doubling of frailty results in a doubling of the hazard of dementia. As expected due to the simulation set up, when all individuals had their frailty set to 1 (i.e. no joint frailty), the hazard ratio per 10mmHg higher systolic BP was 1.00 at all ages. In our most extreme scenario, we simulated a frailty variance of 1. With this frailty distribution, patients who died aged 40-50 had a mean frailty of 1.88, compared to 0.38 amongst patients dying aged 90 or older, meaning their hazard of dementia in such patients was nearly 5 times higher (i.e. 1.88/0.38). We believe that this is a fairly extreme simulated co-dependence between the underlying hazard of dementia and death. Under this scenario, the estimated HR per 10mmHg higher systolic BP for dementia was 0.96 amongst patients aged <70, 0.93 amongst those aged 70-85 and 0.92 amongst patients aged over 85.

**Appendix Figure**: Kaplan Meier curves of actual and simulated rates of dementia and death (for simulation with no joint frailty)



**Appendix Table:** Comparison of hazard ratios for dementia according to degree of dependence between dementia and death

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Increasing joint frailty (co-dependence between death and dementia) from left to right 🡪** | | | | | |
|  | No joint frailty | Alpha=0.2 | Alpha=0.4 | Alpha=0.6 | Alpha=0.8 | Alpha=1.0 |
| **Estimated hazard ratio per 10mmHg higher long-term average systolic blood pressure (95% CI)** | | | | | |  |
| Aged <70 | 0.999  (0.986 to 1.011) | 0.988  (0.976 to 1.001) | 0.996  (0.984 to 1.008) | 0.962  (0.951 to 0.974) | 0.982  (0.971 to 0.994) | 0.961  (0.950 to 0.972) |
| Aged 70-85 | 1.000  (0.995 to 1.004) | 0.977  (0.972 to 0.981) | 0.958  (0.953 to 0.962) | 0.948  (0.943 to 0.953) | 0.936  (0.931 to 0.941) | 0.930  (0.925 to 0.934) |
| Aged >85 | 0.999  (0.993 to 1.004) | 0.950  (0.945 to 0.956) | 0.920  (0.915 to 0.926) | 0.911  (0.905 to 0.916) | 0.914  (0.908 to 0.919) | 0.917  (0.911 to 0.923) |
| **Mean frailty for dementia by decade of death** | | | | | | |
| 40-50 | 1.00 | 1.19 | 1.39 | 1.57 | 1.73 | 1.88 |
| 50-60 | 1.00 | 1.19 | 1.37 | 1.53 | 1.67 | 1.79 |
| 60-70 | 1.00 | 1.17 | 1.31 | 1.44 | 1.54 | 1.63 |
| 70-80 | 1.00 | 1.11 | 1.19 | 1.25 | 1.28 | 1.29 |
| 80-90 | 1.00 | 0.99 | 0.96 | 0.92 | 0.87 | 0.82 |
| 90+ | 1.00 | 0.75 | 0.59 | 0.49 | 0.43 | 0.38 |