# Appendices

# Appendix 1

*Flow diagram indicating the number of patients in the study across time points*

Deceased = 2

No further data = 21

Deceased = 1

No further data = 10

Deceased = 2

No further data = 17

Baseline

n = 164

2 years

n = 122

3 years

n = 111

1 year

n = 141

# Appendix 2

*Linear mixed model examining the difference between standardised apathy and depression scores over time*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Estimate** | **95% CI** | **t-value** | **df** | **Sig** |
| Intercept1 | -0.2 | -1.4, 1.1 | -0.3 | 159.7 | 0.770 |
| Time effect2 | 0.1 | 0.0, 0.2 | 2.9 | 186.6 | **0.005** |
| Age | 0.0 | 0.0, 0.0 | 0.5 | 158.2 | 0.631 |
| Sex (female) | -0.4 | -0.6, -0.2 | -3.3 | 164.1 | **0.001** |
| Antipsychotic | 0.1 | -0.3, 0.6 | 0.6 | 472.7 | 0.521 |
| Antidepressant  | -0.1 | -0.3, 0.2 | -0.6 | 386.5 | 0.521 |
| Number of medications | 0.0 | 0.0, 0.0 | -1.0 | 253.3 | 0.296 |
| Incident dementia | 0.2 | 0.0, 0.5 | 1.9 | 555.5 | 0.058 |

Note. Time effect indicates the difference between z-score of apathy minus the z-score of depression over time. Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 Random effect with mean -0.2 and SD = 0.5.

2 Random effect with mean 0.1 and SD = 0.2.

# Appendix 3

*Linear mixed model examining apathy as a predictor of dementia severity over time*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | 0.2 | 0.1, 0.2 | 7.5 | 709.4 | **<0.001** |
| Depression | 0.0 | -0.1, 0.0 | -1.5 | 690.7 | 0.129 |
| Age | 0.0 | 0.0, 0.1 | 1.5 | 133.1 | 0.126 |
| Sex (female) | 0.0 | -0.4, 0.5 | 0.2 | 140.6 | 0.868 |
| Antipsychotic | 0.0 | -0.7, 0.7 | -0.1 | 639.3 | 0.955 |
| Antidepressant | 0.2 | -0.2, 0.7 | 1.1 | 390.3 | 0.255 |
| Number of medications | 0.1 | 0.0, 0.1 | 2.3 | 275.0 | **0.022** |
| Incident dementia (at time of MCI diagnosis) | 0.1 | -0.6, 0.8 | 0.3 | 701.3 | 0.765 |
| Time effect for MCI2 | 0.4 | 0.2, 0.6 | 4.6 | 175.4 | **<0.001** |
| Time effect for incident dementia3 | 1.1 | 0.9, 1.4 | 8.4 | 577.8 | **<0.001** |

Note. Dementia severity was assessed using the Clinical Dementia Rating (CDR) scale scored using the sum of boxes. Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 The interaction between time and incident dementia had a p-value of < 0.001 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

2 Random effect with mean 0.4 and SD = 0.9.

3 Random effect with mean 1.1 and SD = 0.9.

# Appendix 4

*Linear mixed model examining apathy as a predictor of neuropsychiatric symptoms (total NPI minus apathy and depression) over time*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | 1.0 | 0.8, 1.2 | 8.9 | 794.2 | **<0.001** |
| Depression | 0.7 | 0.5, 1.0 | 5.4 | 766.6 | **<0.001** |
| Age | -0.2 | -0.3, 0.0 | -2.0 | 144.5 | 0.052 |
| Sex (female) | -0.3 | -2.6, 2.0 | -0.3 | 148.5 | 0.770 |
| Antipsychotic | 3.2 | -0.3, 6.8 | 1.8 | 671.6 | 0.076 |
| Antidepressant | 0.4 | -1.6, 2.4 | 0.4 | 477.7 | 0.678 |
| Number of medications | 0.3 | 0.0, 0.5 | 2.0 | 296.0 | **0.047** |
| Incident dementia (at time of MCI diagnosis) | -3.3 | -6.7, 0.0 | -1.9 | 776.0 | 0.053 |
| Time effect for MCI2 | 0.4 | -0.2, 1.0 | 1.4 | 194.3 | 0.154 |
| Time effect for incident dementia3 | 2.9 | 1.7, 4.1 | 4.9 | 689.5 | **<0.001** |

Note. Neuropsychiatric symptoms were assessed using the total Neuropsychiatric Inventory (NPI) minus apathy and depression. Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 The interaction between time and incident dementia had a p-value of < 0.001 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

2 Random effect with mean 0.4 and SD = 0.9.

3 Random effect with mean 1.1 and SD = 0.9

# Appendix 5

*Linear mixed model examining apathy at baseline as a predictor of clinical outcomes*

***Function***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | -0.7 | -1.3, -0.1 | -2.3 | 131.6 | **0.022** |
| Depression | -0.2 | -0.8, 0.4 | -0.6 | 138.7 | 0.580 |
| Age | -0.1 | -0.3, 0.0 | -1.5 | 132.4 | 0.146 |
| Sex (female) | 2.7 | 0.1, 5.2 | 2.1 | 137.5 | **0.039** |
| Antipsychotic | 0.3 | -2.4, 3.0 | 0.2 | 729.8 | 0.828 |
| Antidepressant | -1.2 | -3.0, 0.6 | -1.3 | 661.0 | 0.198 |
| Number of medications | -0.2 | -0.5, 0.0 | -2.1 | 416.0 | **0.037** |
| Incident dementia (at time of MCI diagnosis) | -0.5 | -2.8, 1.8 | -0.4 | 658.2 | 0.673 |
| Time effect for MCI2 | -2.5 | -3.2, -1.8 | -7.0 | 169.5 | **<0.001** |
| Time effect for incident dementia3 | -4.0 | -5.0, -3.0 | -7.9 | 470.4 | **<0.001** |

*Note.* Function was assessed using the Functional Autonomy Measurement System (SMAF). Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 The interaction between time and incident dementia had a p-value of <0.001 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

2 Random effect with mean -2.5 and SD = 3.7

3 Random effect with mean -4.0 and SD = 3.7

***Dementia Severity***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | 0.1 | 0.0, 0.2 | 2.0 | 125.9 | **0.046** |
| Depression | 0.0 | -0.1, 0.1 | -0.1 | 133.3 | 0.926 |
| Age | 0.0 | 0.0, 0.1 | 1.4 | 126.4 | 0.168 |
| Sex (female) | -0.1 | -0.6, 0.4 | -0.3 | 133.4 | 0.776 |
| Antipsychotic | 0.0 | -0.8, 0.7 | -0.1 | 658.2 | 0.959 |
| Antidepressant | 0.3 | -0.2, 0.7 | 1.2 | 390.4 | 0.217 |
| Number of medications | 0.1 | 0.0, 0.1 | 1.9 | 271.7 | 0.052 |
| Incident dementia (at time of MCI diagnosis) | 0.2 | -0.5, 0.9 | 0.6 | 702.3 | 0.550 |
| Time effect for MCI2 | 0.5 | 0.3, 0.7 | 5.0 | 172.9 | **<0.001** |
| Time effect for incident dementia3 | 1.2 | 0.9, 1.5 | 8.6 | 550.0 | **<0.001** |

Note. Dementia severity was assessed using the Clinical Dementia Rating (CDR) scale scored using the sum of boxes. Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 The interaction between time and incident dementia had a p-value of < 0.001 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

2 Random effect with mean 0.5 and SD = 0.9.

3 Random effect with mean 1.2 and SD = 0.9.

***Cognition***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | 0.0 | -0.1, 0.2 | 0.3 | 133.9 | 0.775 |
| Depression | -0.1 | -0.3, 0.0 | -1.6 | 144.6 | 0.114 |
| Age | -0.1 | -0.1, 0.0 | -2.4 | 133.2 | **0.017** |
| Sex (female) | -0.7 | -1.4, 0.0 | -2.0 | 141.4 | **0.047** |
| Antipsychotic | 0.6 | -0.5, 1.8 | 1.1 | 605.4 | 0.267 |
| Antidepressant | -0.1 | -0.8, 0.6 | -0.3 | 375.3 | 0.790 |
| Number of medications | 0.0 | -0.1, 0.1 | 0.4 | 260.7 | 0.665 |
| Incident dementia (at time of MCI diagnosis) | -0.8 | -1.9, 0.2 | -1.6 | 673.1 | 0.115 |
| Time effect for MCI2, 3 | -0.7 | -1.0, -0.5 | -5.4 | 150.0 | **<0.001** |
| Time effect for incident dementia4 | -1.2 | -1.6, -0.8 | -5.6 | 589.6 | **<0.001** |

Note. Cognition was assessed using the Mini-Mental State Examination (MMSE). Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 Refers to patients who subsequently developed dementia

2 The interaction between time and incident dementia had a p-value of 0.022 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

3 Random effect with mean -0.7 and SD = 1.2

4 Random effect with mean -1.2 and SD = 1.2

***Neuropsychiatric symptoms***

*Linear mixed model examining apathy as a predictor of neuropsychiatric symptoms (total NPI minus apathy and depression)*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | 0.7 | 0.1, 1.2 | 2.2 | 144.0 | **0.030** |
| Depression | 1.5 | 0.9, 2.1 | 4.9 | 150.1 | **<0.001** |
| Age | -0.1 | -0.3, 0.0 | -1.5 | 145.2 | 0.142 |
| Sex (female) | -1.3 | -3.9, 1.2 | -1.0 | 151.3 | 0.306 |
| Antipsychotic | 2.5 | -1.3, 6.3 | 1.3 | 697.5 | 0.198 |
| Antidepressant | 0.2 | -2.1, 2.4 | 0.2 | 484.0 | 0.873 |
| Number of medications | 0.3 | 0.0, 0.5 | 1.8 | 299.1 | 0.075 |
| Incident dementia (at time of MCI diagnosis) | -1.9 | -5.5, 1.6 | -1.1 | 748.5 | 0.284 |
| Time effect for MCI2 | 0.7 | 0.1, 1.4 | 2.2 | 200.0 | **0.033** |
| Time effect for incident dementia3 | 3.2 | 2.0, 4.5 | 5.1 | 682.6 | **<0.001** |

Note. Neuropsychiatric symptoms were assessed using the total Neuropsychiatric Inventory (NPI) minus apathy and depression. Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 The interaction between time and incident dementia had a p-value of < 0.001 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

2 Random effect with mean 0.7 and SD = 2.5.

3 Random effect with mean 3.2 and SD = 2.5

***Caregiver Burden***

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Effect Estimate**  | **95% CI** | **t-value** | **df** | **Sig** |
| Apathy  | 1.7 | 0.8, 2.6 | 3.8 | 146.1 | **<0.001** |
| Depression | 0.3 | -0.6, 1.2 | 0.6 | 153.0 | 0.548 |
| Age | -0.1 | -0.4, 0.1 | -1.0 | 145.8 | 0.306 |
| Sex (female) | -1.2 | -5.0, 2.6 | -0.6 | 150.8 | 0.541 |
| Antipsychotic | -2.7 | -7.2, 1.7 | -1.2 | 773.2 | 0.232 |
| Antidepressant | 2.2 | -0.6, 5.1 | 1.5 | 618.7 | 0.125 |
| Number of medications | 0.2 | -0.1, 0.6 | 1.3 | 402.9 | 0.208 |
| Incident dementia (at time of MCI diagnosis) | 0.3 | -3.6, 4.2 | 0.2 | 696.5 | 0.874 |
| Time effect for MCI2 | 1.9 | 1.0, 2.7 | 4.3 | 178.7 | **<0.001** |
| Time effect for incident dementia3 | 3.0 | 1.6, 4.5 | 4.1 | 566.8 | **<0.001** |

Note. Caregiver burden was assessed using the Zarit Burden Inventory (ZBI). Numbers in bold indicate p-values < 0.05. Sex indicates values for females relative to males.

1 The interaction between time and incident dementia had a p-value of 0.118 and was retained in the model. As such, separate time effects for the presence and absence of dementia are reported, while the intercept term is not reported.

2 Random effect with mean 1.9 and SD = 3.5

3 Random effect with mean 3.0 and SD = 3.5