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Long-term medical costs of Alzheimer's disease: matched cohort analysis

Elizaveta Sopina[1]*, Eldon Spackman[2], Janne Martikainen[3], Gunhild Waldemar[4] & Jan Sørensen[1,5]

[1] PhD, Danish Centre for Health Economics (DaCHE), Department of Public Health, University of Southern Denmark
[2] PhD, Department of Community Health Sciences, The University of Calgary, Canada
[3] PhD, School of Pharmacy, The University of Eastern Finland, Kuopio, Finland
[4] DMSc, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark.
[5] MA, MSc, Healthcare Outcomes Research Centre, Royal College of Surgeons in Ireland, Dublin, Ireland

* Corresponding author

e-mail: lsopina@health.sdu.dk
tel.: +45 65 50 83 84
Address: J.B. Winsløws Vej 9, Odense, Denmark 5000

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Abstract

Objectives

Medical costs associated with Alzheimer's Disease (AD) are characterised by uncertainty and often presented in a format unsuitable for decision modelling. We set out to estimate long-term medical costs attributable to AD compared to the general population for use in decision modelling.

Methods

We used multiple logistic regressions to generate propensity scores to match 26,951 incident cases of AD with 26,951 people without AD, identified from Danish hospital and medication registries. Costs were available for up to 11 years for each individual, representing costs for ten years before and five years after diagnosis. Generalised estimating equations were employed to investigate the effect of having AD on primary care, medication, hospital and total costs in the matched cohort. We also explored the impact of other socio-economic and demographic factors on healthcare costs.

Results

We report costs by year to diagnosis, from ten years before to five after. AD was associated with significantly higher costs, driven by medication and hospital costs, especially around the time of diagnosis. Mean total medical cost was €4,996 higher for AD than for the control group in year of diagnosis, after which primary and hospital costs decreased to pre-diagnostic levels. AD had higher attributable primary care costs in years preceding diagnosis.

Conclusions

Reporting AD-attributable costs by year to diagnosis can be useful for use in decision-modelling. Medical costs attributed to AD are driven by diagnostic procedures and medication, and the impact of AD on medical costs may not be as high or prolonged as previously suggested.

Keywords: Alzheimer's disease, medical costs, matched cohort, registry study

Introduction

Alzheimer's disease (AD) is the most common type of dementia, accounting for approximately 60 percent of all people with dementia [1]. It is a chronic condition that disproportionally afflicts the elderly and is characterised by the decline of cognitive functions and affects the person's ability to perform everyday tasks [1]. AD is often associated with high medical costs, and the increase in dementia – and AD – prevalence due to ageing populations is expected to put significant pressure on health systems [2, 3]. Efficient allocation of healthcare resources in this area has become a priority for policy makers [4].

Cost estimates of AD vary dramatically, depending on the setting, the perspective and the method used to estimate them. In a systematic review of AD costs, Schaller et al. report community-based costs vary between US$3,000 and $18,000 per person per year [5]. Another systematic review of AD costs in Europe reported a variation between €6,000 and €64,000 [6]. The reason for such variation can be attributed to the setting in which the costs occur, but are also due to a number of methodological issues, which have been previously documented, including classification of costs [5, 7], measuring and valuing resources [6].

Economic evaluation, and in particular decision-analytic modelling, help inform resource allocation decisions, but do require a certain level data accuracy to produce informative results. While average annual estimates, such as described above, might be useful for indicating the economic burden of AD, they are less helpful in application for economic evaluation, and in particular, decision-analytic modelling [7].

Costs associated with AD/dementia are often collected over a short period of time [7], and are presented as total (annual) costs, without showing how costs change as the disease progresses. In a recent systematic review of 27 studies [5], more than a third of included studies did not differentiate between different stages of the disease, and among those who did, seven different methods were used to define disease progression.

Decision modelling often compares healthcare costs between people with and without AD. A systematic review of 16 cost studies found that only two reported costs for non-dementia controls [6]. Comparison of costs in AD and control groups is also important in order to ascertain that costs are not simply reflecting the effect of ageing on utilisation of health care [2].

Cost estimates also often include societal and informal costs, as well as direct medical costs [6]. Decision modelling often requires inputs specific to the level of care provided (primary, secondary, etc), and presenting associated costs as a total does not provide sufficient detail. Total costs, inclusive of residential and informal costs, may also be less relevant if economic evaluation takes a health system perspective. This compromises the suitability of such cost estimates for use in decision modelling.

In this study, we set out to estimate direct medical costs attributable to AD, and to describe progression of these costs over time for use in decision modelling.

Methods

Study population

The study population was extracted by the Statistics Denmark's Research Service [8]. The AD group was identified from hospital and pharmaceutical registries using a previously established algorithm [9] and represents all people with an AD diagnosis in Denmark from 2004 to 2010 who were living in the community setting at the time of diagnosis. Patients were included in the AD group from the hospital

registry if they were discharged from hospital (or after an outpatient visit) with a primary or secondary ICD-10 code consistent with AD (G30*, F00*). Patients were included from the pharmaceutical registry if their pattern of prescriptions was consistent with an AD diagnosis (ATC codes N06DA02, N06DA04, N06DX01 and N06DA03, corresponding to 'Donepezil', 'Galantamine', 'Memantine' and 'Rivastigmine'). The date of diagnosis was defined as either the first AD-related hospital admission or date of the first relevant prescription, whichever occurred earlier. We used a wash-out period of one year to ensure only incident cases of AD were included in the study, thus only including cases diagnosed on or after 01.01.2005. The control group without any dementia-related diagnoses was obtained through a random sample of 30% of the entire Danish population on 01.01.2004 (AD cases described above were excluded from this sample) by Statistics Denmark [8].

Charlson comorbidity index (CCI) score [10, 11] was calculated using national hospital registry database (LPRPOP) [8] for individuals in both groups for the period of 01.01.1996-31.12.2003. We also retrieved individual information on region of residence (one of the five regions of Denmark), type of accommodation (owned or rented), living arrangement (whether living alone or with partner/caregiver), as well as education (primary and lower secondary/upper secondary/bachelor and short tertiary/master or higher), all as of 01.01.2004. Education information was only available for people born in or after 1920; for those born before 1920 it was coded as 'unclassified'. All people who migrated to another country during the study period were excluded from analysis. All people aged less than 50 on 01.01.2004 were excluded due to low prevalence of AD in this age group.

Cost data

All primary, secondary and tertiary healthcare is free of charge to Danish residents [12], and reimbursed prescription medications are subsidised progressively with increasing annual expenditure, with maximum annual out-of-pocket expenditure capped at approximately €500 per person [13]. The costs included in the analysis represent a Health System perspective.

The cost data was obtained from the following national registers: primary care reimbursement (all primary care costs, including general practitioner care, laboratory/diagnostic costs, dentistry, and other ancillary care such as physio, ophthalmology, etc.), pharmaceutical (all community-dispensed prescriptions, including both the out-of-pocket co-payment and the government subsidy) and hospital (combining all in- and out-patient visits) [8], all for the period from 2000 to 2010. The costs were categorised into three groups: primary, medication and hospital. All costs were re-expressed in 2016 Danish Crowns (DKK) using the Consumer Price Index (CPI) [14] and then converted to 2016 Euro (1€ = 7.44 DKK).

Matching

Using observational data for comparing health care utilisation in groups of people with and without a disease can produce flawed findings, as people who have a condition such as AD are likely to differ significantly from those who do not. These differences can affect the estimations produced by observational data [15]. This problem can be addressed by reducing any relevant covariates that can predict developing AD to a single propensity score (the likelihood of having AD), and matching an intervention and control group on this score. Propensity score matching helps reduce bias in observational data, allowing for a more balanced sample and improving the precision of estimates by mimicking randomisation [15, 16]. The probability of having AD (the propensity score) was estimated using multiple logistic regression. The model consisted of confounders associated with an increased risk of having AD,

identified from literature: age [1], gender [1, 17], education [17-19], co-morbidities (CCI score) [20, 21], living arrangement (alone or with a partner/caregiver) [22] and income [1, 19]. In addition, the region of Denmark where study subjects resided at the beginning of the study period were included (2004) in order to ensure a balanced sample. Accommodation status (renting or owning) was also recorded at the start of the study as a measure of socio-economic status, in addition to income.

One-to-one nearest-neighbour matching with no replacement was conducted [23] by year of diagnosis in order to avoid confounding. Data for each incident year (2005 – 2010) was then merged. The distribution of propensity scores, and balance in the confounding factors was compared by AD and control groups before and after matching. Reduction of bias in the matched sample was tested with chi-squared and t-tests, as appropriate, as well as by comparing reduction in standardised differences [24]. All unmatched cases were excluded from further analyses.

Statistical analyses

Once matched, longitudinal data was used to estimate costs according to the time from the year of diagnosis (from ten years before, to five years after). Persons who died during the observation period were censored. For controls this was done based on the year of diagnosis for the nearest-neighbour AD case they were matched with. For the AD group, age at diagnosis was calculated at the first date of AD-related contact with the health system, for controls it was the age on the date of diagnosis for their matched AD pair. Finally, the mean primary, medication, hospital and total cost by year from diagnosis were estimated for AD and control groups.

The associations of AD and other covariates with primary, medication, hospital and total costs were analysed using Generalised Estimating Equations (GEEs) to reflect the panel structure of the data. In the GEE models, we controlled for the interaction of having AD with the year of the cost (from 10 years before to 5 years after diagnosis), as well as age at diagnosis, gender, CCI score, income (in tens of thousands of Euro), education, home ownership, living alone or with a partner and region of Denmark. The applied GEE models with primary, medication, hospital or total costs as the dependent variable were specified with a Gamma distribution and a logit link function. An independent covariance matrix was selected based on QIC selection criterion [25]. All statistical analyses were conducted using Stata 14 [26].

Results

We identified 26,968 incident cases of AD, diagnosed between 01.01.2005 and 31.12.2010, of these 26,951 were successfully matched to an equivalent number of non-AD controls; 17 AD cases could not be matched and had to be excluded from analysis. Of the matched AD cases, 44% (11,920) were identified only from the medication registry, with the rest identified from both hospital and medication registries. The matching process successfully reduced the variation in propensity score distribution between the two groups (Supplementary Figure 1, Supplementary Figure 2). The differences between AD and controls in all included confounders, which were significantly different before matching, were reduced to statistically insignificant levels after matching (Table 1; supplementary Figure 3).

The mean primary, medication, hospital and total costs for people with AD and controls are reported by year of diagnosis in Figure 1 and Supplementary Table 1. In the control group, primary care costs increase steadily across the 16 years of observation, almost doubling from €277 in year -10 to €501 in year 5. A similar increase in primary care costs can also be observed for the AD group until the index year (the year of

diagnosis), after which the costs declined. Overall, the AD group has consistently higher mean primary care costs than the control group until the third year after diagnosis.

The mean medication cost for the control group was €669 in year -10, and increased to €993 in year 0, followed by a slight decline to €953 in year 5. The AD group had similar, although somewhat higher, costs compared to controls in year -10 (€672), with the difference becoming more pronounced each year until year -1 (€985 for controls, €1,131 for AD). The mean medication costs for the AD group more than doubled in year 0, reaching €2,466, and further increasing to €3,012 in year after diagnosis, followed by a slight decline to €2,729 in year 5.

Overall, the hospital costs of the control group demonstrate a steady increase over the 16 years of observation, increasing from €1,100 in year -10, to €5,883 in year 5, by an average of €230 a year. AD group experienced more variation in their hospital costs: costs in years -10, -9 and -8 (€1,227, €1311 and €1371, respectively) were slightly higher than the control group, but were then overtaken by the control group in years -4 to -2, after which the AD group experienced a large increase in years around diagnosis, peaking at €6,413 in year 0 (almost double that of the control group), and falling again to below the mean cost of the control group in year 3 after diagnosis.

As primary care costs comprise a relatively small proportion total cost, the pattern of total healthcare costs across the observation period was mostly driven by the changes in medication and hospital costs. The total costs rose steadily and consistently for the control group, almost tripling from €2,046 in year -10 to €5,883 in year 5. Over the 10 years preceding diagnosis, the AD group experienced somewhat higher mean total costs than the control group, with costs for both groups rising steadily each year; total costs rose sharply for the AD group one year before diagnosis, peaking in the year of diagnosis (€9,411 for AD compared to €4,919 for control group), and receding to around €6,500 in years 3 onwards, although remaining higher than the mean total cost for the control group.

The results from GEE models are presented in Table 2, the estimates are exponentiated, and represent the mean ratio between the compared and reference group. Being female was associated with a 12% higher (p<0.001) primary care and 13% (p<0.001) higher medication costs, 14% lower (p<0.001) hospital, and 4% lower (p<0.001) total costs than males. One year increase in the age at diagnosis was associated with a 0.5% (p<0.001) increase in primary, 1.7% increase in secondary and 0.9% increase in total costs over the 16 years of observation (p<0.001). Higher CCI scores were associated with overall higher costs across all three cost categories. Individuals with higher levels of education than primary school experienced significantly higher total costs, from 4% for secondary school, to 8% for Bachelor degree and higher (p<0.001).

Income had a small significant effect on primary, secondary and medication costs, but no effect on total costs. Owning a home was associated with consistently lower costs across all three categories with a 4% reduction in primary (p<0.001), and 10% reduction in secondary, medication and total costs (p<0.001), compared to people who resided in rental accommodation. Living with a partner or caregiver did not have a significant effect on medication or total costs, although those who did live with a partner had 10% higher primary care costs (p<0.001) and 5% lower hospital costs (p<0.001) compared to those who lived alone. Compared to the Capital region, the other four regions incurred higher medication costs, but lower primary, hospital and total costs. The difference in total costs was 5% lower than the capital region in Zealand and Southern Denmark (p<0.001), 8% lower in North Denmark (p<0.001) and 11% lower in Central Denmark (p<0.001).

Using the GEE models, health care costs attributable to AD for each cost category and year of follow up were estimated (Supplementary Table 2; Figure 2; Figure 3). Primary care costs were significantly higher for

people with AD than for controls until the year after diagnosis, after which the difference between the two groups became small and not statistically significant. Medication costs were higher for the AD group for all but the first year of observation, although the attributable costs increased from around €100 in years before diagnosis, to over €2,000 in years after diagnosis. Hospital costs were somewhat higher for the AD group (between €90 and €193) in years -8 to -5, after which the difference was small and insignificant. AD-attributable costs increased significantly to €911 one year before diagnosis, reaching €3,417 in year of diagnosis, and falling to insignificant levels again two years after diagnosis.

Total costs were significantly different for years -9 to -4, where the AD group accrued higher costs than the control group, with differences ranging between €137 and €313. The difference between the two groups became insignificant three and two years prior to diagnosis. Total costs attributable to AD became more pronounced one year prior to diagnosis, reaching €1,114 and further rising to €4,996 in the year of diagnosis, falling to €902 in year 5, with all differences being statistically significant.

Discussion

While there currently is no treatment for AD, the number of interventions, both pharmaceutical [27, 28] and non-pharmaceutical [29], has been growing in the past two decades, with further expected developments [30]. While there is some evidence of effectiveness, the opportunity cost of new interventions needs to be assessed through economic evaluation before investment is made. Decision modelling is a helpful tool in conducting economic evaluations, as it moves beyond trial-based evaluations by enabling data synthesis, inclusion of multiple comparisons and an appropriate time horizon, and allowing for quantification of uncertainty. However, to produce valid estimates, decision models require accurate data inputs. One of the key inputs that creates uncertainty in economic decision models is the cost of treatment.

In this study, we set out to establish the attributable medical costs of Alzheimer's Disease for use in decision modelling. Like previous studies [5, 7, 31, 32], our findings suggest that that AD is associated with significant high medical costs. Our study estimated, with some precision, the extent to which these costs can be attributed to AD itself, rather than to other differences between people with and without AD.

Overall, our estimates of AD-attributable costs are lower than previously reported: a recent study found the average annual medical costs of €5,800 for AD and €3,250 for controls [33]; other studies report medical cost differences of similar magnitude [34-36]. Such differences are comparable to our findings around the time of diagnosis. However, our data show that this difference does not persist, with differences in costs between the two groups dropping to 25% three years after diagnosis and to 15% five years after diagnosis. This could potentially be due to the fact that in this study, we were unable to account for transition from community to residential setting, where admission to hospital may decline, thus reducing the costs [36].

These differences are the result of viewing costs in a longitudinal way, which allowed us to control for ageing of the cohort, and to isolate the attributable and observed costs. When controlled for co-morbidities and socio-demographic factors, the GEE model predicts that costs for AD and control groups increase over the observation period (Figure 2). Attributable costs (Supplementary Table 2, Figure 2, Figure 3), however, remain flat, and increase only around the time of diagnosis; similar findings were reported by Lin et al. [37].

Unsurprisingly, primary care costs comprise a relatively small proportion of the total costs. However, the pattern of primary care costs is rather interesting: AD group experience consistently and significantly higher costs than the control group until the year of diagnosis, after which the difference decreases and becomes

insignificant. It is possible, that this reduction is the result of having the healthcare needs met through being diagnosed and receiving treatment. Alternatively, this could be an artefact of having the AD diagnosis masking any other underlying healthcare needs, or a reflection of unmet medical care needs.

Attributable costs of medication change over the observation period in a more intuitive way: the AD had marginally higher costs which then tripled that of the control group around the time of diagnosis, and remained at a high level until the end of the follow-up period, reflecting the high cost of the anti-dementia and other associated medication. Overall, our estimates of medication costs for people with AD were comparable with findings of a recent German study [38].

Hospital costs accounted for around half of the total expenditure, similar to some other studies [39-41]. These had a similar pattern to that of primary care costs: increasing significantly a year before, peaking in the year of diagnosis, and returning to the same level around 3 years after diagnosis. This peak in attributable hospital expenditure could be ascribed to procedures associated with the diagnosis of AD [42].

Having comorbidities, measured by CCI, was found to be strongly associated with higher expenditure across all three categories. This is an intuitive finding, and one supported by previous studies, which found that a higher level of comorbidity was associated with a significant increase in expenditure by AD groups [41, 43, 44] .

Females had significantly higher (around 12%) primary and medication costs and lower (around 13% hospital costs) than males. This is in line with previous findings that women utilise less formal care [33], although it is not entirely clear how.

The study findings suggest that, compared to the Capital Region, people in the other four regions in Denmark accrued significantly lower (between 13 to 15%) primary and hospital costs, and higher (between 3 and 8%) medication costs. These differences could be explained by higher density of population and closer proximity to primary and hospital care providers in the Capital region compared to the rest of the country. However, further investigation into these differences could help shed light on these differences.

Strengths and limitations

One of the key strengths of this study are the large sample size and accuracy of the data. The accuracy of the Danish registries has been found consistently high for dementia/AD diagnoses [9], CCI [45] as well as the prescription registry [46], and the use of patient registries has been shown to be an overall effective tool for healthcare cost studies [47]. The use of registry data also allows for an unprecedented, to the best of our knowledge, 16 years of follow up.

Observational data imposes a number of limitation in terms of imbalances between the intervention and control groups. While avoiding the effect of unobserved confounders is impossible, the matching procedure employed in our study created a well-balanced group. Having a large sample sile allowed us to sacrifice additional controls that could be obtained by one-to-many matching approaches to maintain the balance between the two groups [23].

A major challenge of using cost data from published literature is that model data needs to be linked to clinical data using the same disease indicators, which is often difficult, if not impossible [6]. The varied purpose of disease indicators (such as cognitive, behavioural or functional) and the large number of indicators used in trials further exacerbates this issue. This makes a compelling argument for reporting costs in a more straightforward and easily-applied way, where costs can be mapped on to other indicators. In our view, years from diagnosis addresses these issues, as it can easily be mapped on to clinical disease indicators, and is not restricted to any single aspect of the disease.

The findings of this study are also subject to some limitations. The study focused solely on medical costs of community-dwelling people with AD, and the costs of residential and informal care were not captured, partially due to data availability. It is well documented that residential/nursing home and informal care comprise a significant part of total cost of AD [5], and therefore our findings should be viewed as analysing only the medical, not total, costs of AD.

Another potential limitation of this study is that the included AD population is comprised solely of individuals who have received a formal diagnosis. It is recognised that AD is significantly underdiagnosed [1, 22]. It is also possible that people with AD were diagnosed, but under a different classification (such as 'generalised dementia', for example), and thus were not included in our study population. However, there is evidence to suggest that there is little cost difference between diagnosed and undiagnosed people with dementia outside of medication costs [48]. There is also a risk that the non-AD dementia cases were included in the control group due to a lack of clear diagnosis.

Conclusions

In the present study, we estimated longitudinal medical costs attributable to AD, compared to a matched control group. Total medical costs for people with AD were double that of people without AD around the time of diagnosis, with primary and hospital costs returning to insignificantly different levels three years after diagnosis. Medication was the main driver of cost after the diagnostic period. These findings suggest that medical costs attributed to AD are driven by diagnostic procedures and medication, and the impact of AD on medical costs may not be as high or prolonged as previously suggested.

References

1. Alzheimer's Association, *2016 Alzheimer's disease facts and figures.* Alzheimer's & Dementia, 2016. **12**(4): p. 459-509.
2. Wimo, A., et al., *The worldwide economic impact of dementia 2010.* Alzheimer's & Dementia, 2013. **9**(1): p. 1-11.e3.
3. Wu, Y.-T., et al., *Dementia in western Europe: epidemiological evidence and implications for policy making.* The Lancet Neurology, 2016. **15**(1): p. 116-124.
4. Prince, M., et al., *World Alzheimer report 2016: improving healthcare for people living with dementia: coverage, quality and costs now and in the future.* 2016.
5. Schaller, S., et al., *The main cost drivers in dementia: a systematic review.* International Journal of Geriatric Psychiatry, 2015. **30**(2): p. 111-129.
6. Jönsson, L. and A. Wimo, *The Cost of Dementia in Europe: A Review of the Evidence, and Methodological Considerations.* PharmacoEconomics, 2009. **27**(5): p. 391-403.
7. Costa, N., et al., *Methodological considerations in cost of illness studies on Alzheimer disease.* Health Economics Review, 2012. **2**(1): p. 18.
8. Danmarks Statistik. *REGISTER- OG VARIABELOVERSIGTER*. 2017 [cited 2017 6 October]; Available from: http://www.dst.dk/da/TilSalg/Forskningsservice/Data/Register_Variabeloversigter.
9. Phung, T.K.T., et al., *Validity of Dementia Diagnoses in the Danish Hospital Registers.* Dementia and Geriatric Cognitive Disorders, 2007. **24**(3): p. 220-228.
10. D'Hoore, W., C. Sicotte, and C. Tilquin, *Risk adjustment in outcome assessment: the Charlson comorbidity index.* Methods of information in medicine, 1993. **32**(5): p. 382-387.
11. Charlson, M., et al., *Validation of a combined comorbidity index.* Journal of Clinical Epidemiology, 1994. **47**(11): p. 1245-1251.
12. The Ministry of Health, *Healthcare in Denmark - An Overview*. 2017.
13. Laegemiddelstyrelsen (the Danish Medicines Agency). *Reimbursement thresholds*. 2017; Available from: https://laegemiddelstyrelsen.dk/en/reimbursement/calculate-reimbursement/reimbursement-thresholds/.
14. Danmarks Statistik. *Consumer Price Index*. 2017; Available from: http://www.dst.dk/en/Statistik/emner/priser-og-forbrug/forbrugerpriser/forbrugerprisindeks.
15. Rubin, D.B., *EStimating causal effects from large data sets using propensity scores.* Annals of Internal Medicine, 1997. **127**(8_Part_2): p. 757-763.
16. Guo, S. and M.W. Fraser, *Propensity score analysis: statistical methods and applications*. 2014: Sage.
17. Letenneur, L., et al., *Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project.* Journal of Neurology, Neurosurgery & Psychiatry, 1999. **66**(2): p. 177-183.
18. Sando, S.B., et al., *Risk-reducing effect of education in Alzheimer's disease.* International journal of geriatric psychiatry, 2008. **23**(11): p. 1156-1162.
19. Evans, D.A., et al., *Education and other measures of socioeconomic status and risk of incident alzheimer disease in a defined population of older persons.* Archives of Neurology, 1997. **54**(11): p. 1399-1405.
20. Biessels, G.J., et al., *Risk of dementia in diabetes mellitus: a systematic review.* The Lancet Neurology, 2006. **5**(1): p. 64-74.
21. Doraiswamy, P.M., et al., *Prevalence and Impact of Medical Comorbidity in Alzheimer's Disease.* The Journals of Gerontology: Series A, 2002. **57**(3): p. M173-M177.
22. Alzheimer's Association, *2012 Alzheimer's disease facts and figures.* Alzheimer's & Dementia, 2012. **8**(2): p. 131-168.
23. Caliendo, M. and S. Kopeinig, *SOME PRACTICAL GUIDANCE FOR THE IMPLEMENTATION OF PROPENSITY SCORE MATCHING.* Journal of Economic Surveys, 2008. **22**(1): p. 31-72.

24. Austin, P.C., *Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples.* Statistics in medicine, 2009. **28**(25): p. 3083-3107.
25. Cui, J. and G. Qian, *Selection of Working Correlation Structure and Best Model in GEE Analyses of Longitudinal Data.* Communications in Statistics: Simulation and Computation, 2007. **36**(5): p. 987-996.
26. StataCorp, *Stata Statistical Software: Release 14*. 2015, College Station, TX: StataCorp LP.
27. Hansen, R.A., et al., *Efficacy and Safety of Donepezil, Galantamine, and Rivastigmine for the Treatment of Alzheimer's Disease: A Systematic Review and Meta-Analysis.* Clinical interventions in aging, 2008. **3**(2): p. 211-225.
28. Mangialasche, F., et al., *Alzheimer's disease: clinical trials and drug development.* The Lancet Neurology, 2010. **9**(7): p. 702-716.
29. Olazarán, J., et al., *Nonpharmacological Therapies in Alzheimer's Disease: A Systematic Review of Efficacy.* Dementia and Geriatric Cognitive Disorders, 2010. **30**(2): p. 161-178.
30. Citron, M., *Alzheimer's disease: strategies for disease modification.* Nature Reviews Drug Discovery, 2010. **9**: p. 387.
31. Frytak, J.R., et al., *Health service utilization among Alzheimer's disease patients: Evidence from managed care.* Alzheimer's and Dementia, 2008. **4**(5): p. 361-367.
32. Zhao, Y., et al., *Healthcare costs and utilization for Medicare beneficiaries with Alzheimer's.* BMC health services research, 2008. **8**: p. 108.
33. Schwarzkopf, L., et al., *Excess costs of dementia disorders and the role of age and gender-an analysis of German health and long-term care insurance claims data.* BMC health services research, 2012. **12**(1): p. 165.
34. Kronborg Andersen, C., et al., *The cost of dementia in Denmark: the Odense Study.* Dementia and geriatric cognitive disorders, 1999. **10**(4): p. 295-304.
35. Rigaud, A.-S., et al., *Patients with Alzheimer's disease living at home in France: costs and consequences of the disease.* Journal of geriatric psychiatry and neurology, 2003. **16**(3): p. 140-145.
36. Taipale, H., et al., *Hospital care and drug costs from five years before until two years after the diagnosis of Alzheimer's disease in a Finnish nationwide cohort.* Scand J Public Health, 2016. **44**(2): p. 150-8.
37. Lin, P.-J., et al., *Medicare Expenditures of Individuals with Alzheimer's Disease and Related Dementias or Mild Cognitive Impairment Before and After Diagnosis.* Journal of the American Geriatrics Society, 2016. **64**(8): p. 1549-1557.
38. Michalowsky, B., et al., *Medication cost of persons with dementia in primary care in Germany.* Journal of Alzheimer's Disease, 2014. **42**(3): p. 949-958.
39. Bynum, J.P.W., et al., *The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use.* Research and Practice in Alzheimer's Disease, 2005. **10**: p. 160-164.
40. Hill, J., et al., *Patterns of healthcare utilization and costs for vascular dementia in a community-dwelling population.* Journal of Alzheimer's disease : JAD, 2005. **8**(1): p. 43-50.
41. Fillit, H., J.W. Hill, and R. Futterman, *Health care utilization and costs of Alzheimer's disease: the role of co-morbid conditions, disease stage, and pharmacotherapy.* Family medicine, 2002. **34**(7): p. 528-535.
42. Waldemar, G., et al., *Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline.* European Journal of Neurology, 2007. **14**(1): p. e1-e26.
43. Kuo, T.C., et al., *Implications of comorbidity on costs for patients with alzheimer disease.* Medical Care, 2008. **46**(8): p. 839-846.
44. Taylor, D.H., et al., *The relative effect of Alzheimer's disease and related dementias, disability, and comorbidities on cost of care for elderly persons.* The journals of gerontology. Series B, Psychological sciences and social sciences, 2001. **56**(5): p. S285-S293.

45. Thygesen, S.K., et al., *The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients.* BMC Medical Research Methodology, 2011. **11**(1): p. 83.
46. Wallach Kildemoes, H., H. Toft Sørensen, and J. Hallas, *The Danish National Prescription Registry.* Scandinavian Journal of Public Health, 2011. **39**(7_suppl): p. 38-41.
47. Kruse, M. and T. Christiansen, *Register-based studies of healthcare costs.* Scandinavian journal of public health, 2011. **39**(7_suppl): p. 206-209.
48. Michalowsky, B., et al., *Healthcare resource utilization and cost in dementia: Are there differences between patients screened positive for dementia with and those without a formal diagnosis of dementia in primary care in Germany?* International Psychogeriatrics, 2016. **28**(3): p. 359-369.

Table 1: Population characteristics, before and after matching								
Variable		**Before Matching**			**After Matching**			
		AD	**Control**	***p-value****	**AD**	**Control**	***p-value****	**Standardised difference reduction (%)**
No. unique individuals		26,968	1,300,810		26,951	26,951		
Age on 01.01.2004	Mean (SD)	76.8 (7.9)	63.9 (10.2)	<0.001	76.8 (7.9)	76.7 (7.9)	0.643	99.8
Age at diagnosis	Mean (SD)	80.4 (7.7)	n/a	n/a	80.4 (7.7)	80.4 (7.7)	1.0	n/a
Female	%	62.7%	63.0%	<0.001	62.7%	62.7%	0.943	97.9
CCI Score	0	74.4%	77.8%	<0.001	74.4%	74.5%	0.226	90.6
	1	18.2%	15.6%		18.2%	18.4%		
	2	7.2%	6.2%		7.2%	7.1%		
	6	0.1%	0.3%		0.1%	0.1%		
Education	Primary/lower secondary	46.2%	37.8%	<0.001	46.2%	46.3%	0.222	95.8
	Upper secondary	24.3%	36.7%		24.3%	24.5%		
	Bachelor	8.0%	15.2%		8.0%	8.0%		
	Master or higher	2.7%	4.5%		2.7%	2.4%		
	Unclassified	18.8%	5.7%		18.8%	18.8%		
Income (2016 €)	Mean (SD)	16,261 (10,364)	23,170 (13,582)	<0.001	16,391 (10,281)	16,264 (10,414)	0.621	98.2
Living in own home		51.0%	67.4%	<0.001	51.0%	50.9%	0.803	99.2
Living alone		50.2%	67.4%	<0.001	50.3%	50.3%	0.925	99.8
Region	Capital Region	30.6%	28.3%	<0.001	30.6%	30.7%	0.988	99.8
	Region Zealand	12.8%	16.2%		12.8%	12.8%		
	Southern Denmark	31.5%	24.8%		31.5%	31.3%		
	North Denmark	13.7%	17.7%		13.7%	13.7%		
	Central Denmark	11.4%	13.0%		11.4%	11.5%		

*** p-values for t-test for continuous and chi-squared for categorical variables**
CCI: Charlson Comorbidity Index

Table 2: Generalised Estimating Equations on medical costs from ten years before to five years after diagnosis

Parameter		Primary		Medication		Hospital		Total	
		Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
	Constant	149.97	(8.5)						
	Control# Year -10 (ref)	1.000	(0.00)	1.000	(0.00)	1.000	(0.00)	1.000	(0.00)
	Control# Year -9	1.036**	(0.02)	1.023	(0.02)	1.075	(0.06)	1.055	(0.03)
	Control# Year -8	1.100***	(0.02)	1.085***	(0.02)	1.100	(0.06)	1.101***	(0.03)
	Control# Year -7	1.163***	(0.02)	1.155***	(0.02)	1.267***	(0.07)	1.219***	(0.04)
	Control# Year -6	1.216***	(0.02)	1.189***	(0.02)	1.339***	(0.07)	1.277***	(0.04)
	Control# Year -5	1.262***	(0.02)	1.229***	(0.02)	1.501***	(0.08)	1.374***	(0.04)
	Control# Year -4	1.351***	(0.02)	1.304***	(0.03)	1.838***	(0.1)	1.582***	(0.05)
	Control# Year -3	1.435***	(0.02)	1.378***	(0.03)	2.171***	(0.12)	1.780***	(0.05)
	Control# Year -2	1.509***	(0.03)	1.429***	(0.03)	2.577***	(0.14)	2.008***	(0.06)
	Control# Year -1	1.595***	(0.03)	1.461***	(0.03)	2.949***	(0.16)	2.208***	(0.07)
	Control# Year 0	1.654***	(0.03)	1.481***	(0.03)	3.531***	(0.2)	2.500***	(0.08)
	Control# Year 1	1.693***	(0.03)	1.481***	(0.03)	3.815***	(0.22)	2.634***	(0.09)
	Control# Year 2	1.753***	(0.03)	1.488***	(0.03)	4.037***	(0.23)	2.740***	(0.09)
	Control# Year 3	1.784***	(0.03)	1.482***	(0.03)	4.318***	(0.26)	2.859***	(0.10)
	Control# Year 4	1.806***	(0.04)	1.437***	(0.03)	4.474***	(0.3)	2.917***	(0.12)
	Control# Year 5	1.868***	(0.05)	1.441***	(0.04)	4.951***	(0.32)	3.134***	(0.13)
	AD# Year -10	1.128***	(0.03)	1.009	(0.03)	1.102	(0.08)	1.079	(0.04)
	AD# Year -9	1.178***	(0.02)	1.127***	(0.03)	1.141**	(0.07)	1.150***	(0.04)
	AD# Year -8	1.235***	(0.02)	1.162***	(0.03)	1.252***	(0.07)	1.221***	(0.04)
	AD# Year -7	1.295***	(0.02)	1.233***	(0.03)	1.354***	(0.08)	1.306***	(0.04)
	AD# Year -6	1.375***	(0.02)	1.328***	(0.03)	1.525***	(0.08)	1.434***	(0.04)
	AD# Year -5	1.448***	(0.03)	1.370***	(0.03)	1.624***	(0.09)	1.508***	(0.05)
	AD# Year -4	1.534***	(0.03)	1.455***	(0.03)	1.834***	(0.1)	1.651***	(0.05)
	AD# Year -3	1.605***	(0.03)	1.554***	(0.04)	2.114***	(0.11)	1.834***	(0.06)
	AD# Year -2	1.683***	(0.03)	1.605***	(0.03)	2.534***	(0.14)	2.063***	(0.06)
	AD# Year -1	1.889***	(0.03)	1.705***	(0.04)	3.828***	(0.2)	2.767***	(0.08)
	AD# Year 0	2.111***	(0.04)	3.836***	(0.08)	6.840***	(0.36)	5.013***	(0.15)
	AD# Year 1	1.822***	(0.03)	4.705***	(0.09)	4.665***	(0.25)	4.142***	(0.12)
	AD# Year 2	1.784***	(0.03)	4.606***	(0.09)	4.250***	(0.23)	3.875***	(0.12)
	AD# Year 3	1.757***	(0.04)	4.517***	(0.1)	4.307***	(0.25)	3.782***	(0.12)
	AD# Year 4	1.762***	(0.04)	4.371***	(0.11)	3.926***	(0.24)	3.538***	(0.12)
	AD# Year 5	1.735***	(0.06)	4.241***	(0.16)	4.365***	(0.34)	3.597***	(0.16)
Age at diagnosis	Age at diagnosis	1.005***	(0.00)	0.997***	(0.00)	1.017***	(0.00)	1.009***	(0.00)
Gender	Female	1.123***	(0.01)	1.126***	(0.01)	0.864***	(0.01)	0.963***	(0.01)
Charlson index score	CCI 1	1.359***	(0.01)	1.770***	(0.02)	2.208***	(0.04)	1.927***	(0.03)
(ref. CCI = 0)	CCI 2	1.301***	(0.02)	1.486***	(0.02)	2.436***	(0.05)	1.960***	(0.03)
	CCI 6	1.206	(0.12)	1.355**	(0.17)	3.348***	(0.42)	2.364***	(0.25)
Education	Upper secondary	1.089***	(0.01)	1.029**	(0.01)	1.029**	(0.02)	1.036***	(0.01)
(ref = Primary)	Bachelor	1.164***	(0.02)	1.068***	(0.02)	1.075	(0.04)	1.087***	(0.03)
	Masters or higher	1.167***	(0.03)	1.152***	(0.04)	1.036	(0.04)	1.080***	(0.03)
	Unclassified	0.932***	(0.01)	0.974**	(0.01)	0.904***	(0.01)	0.920***	(0.01)
Income	(10,000's €)	1.024***	(0.00)	1.012***	(0.00)	0.990***	(0.00)	1.00	(0.00)
Own Home	Own Home	0.963***	(0.01)	0.905***	(0.01)	0.894***	(0.01)	0.906***	(0.01)
Living with partner	Living with partner	1.098***	(0.01)	1.007	(0.01)	0.948***	(0.01)	0.985	(0.01)
Region	Region Zealand	0.830***	(0.01)	1.004	(0.02)	0.962**	(0.02)	0.950***	(0.01)
Ref – Capital region	Southern Denmark	0.824***	(0.01)	1.073***	(0.01)	0.932***	(0.01)	0.947***	(0.01)
	North Denmark	0.867***	(0.01)	1.031**	(0.02)	0.896***	(0.02)	0.916***	(0.01)
	Central Denmark	0.818***	(0.01)	1.081***	(0.02)	0.848***	(0.02)	0.893***	(0.01)
Observations		564,216		562,508		560,248		564,511	
Unique individuals		53,902		53,902		53,902		53,902	

SE: standard error; Ref.: reference category.
***** p<0.01, ** p<0.05**

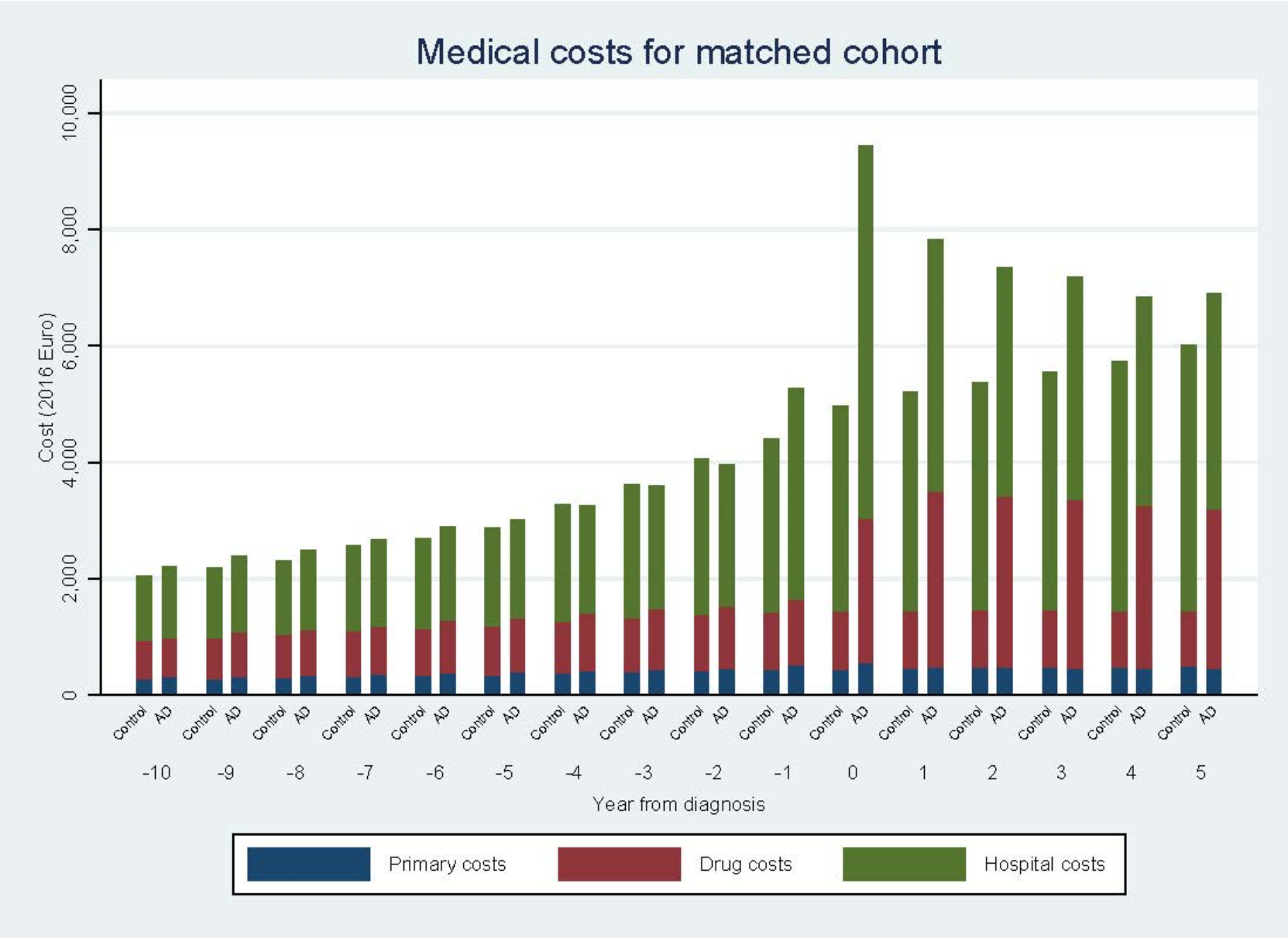


Figure 1: Mean primary, medication and hospital costs by year from diagnosis for matched cohort of incident AD cases (n=26,951) and controls (n=26,951).

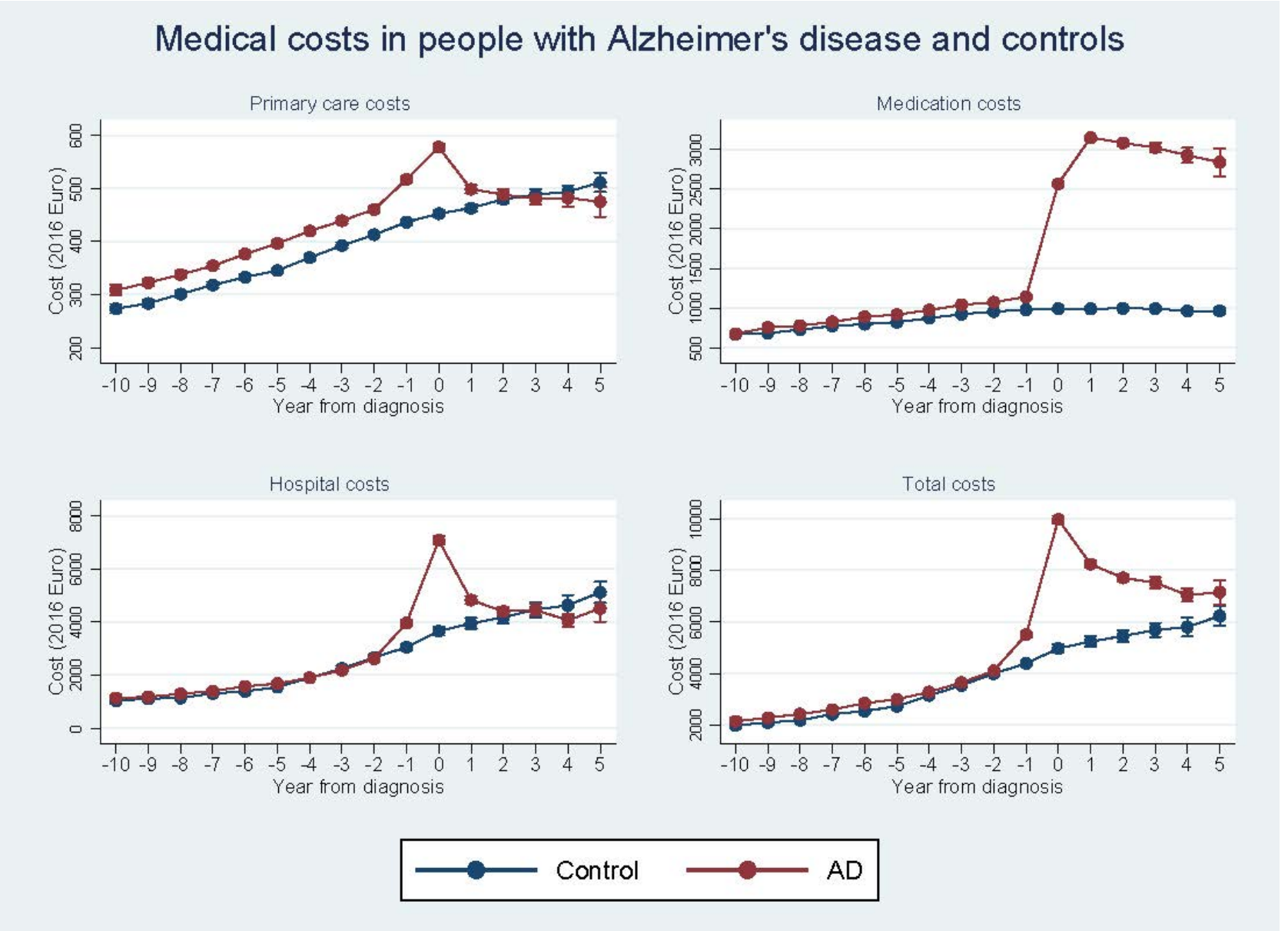


Figure 2: GEE-estimated medical costs for AD and controls over 16 years of observation

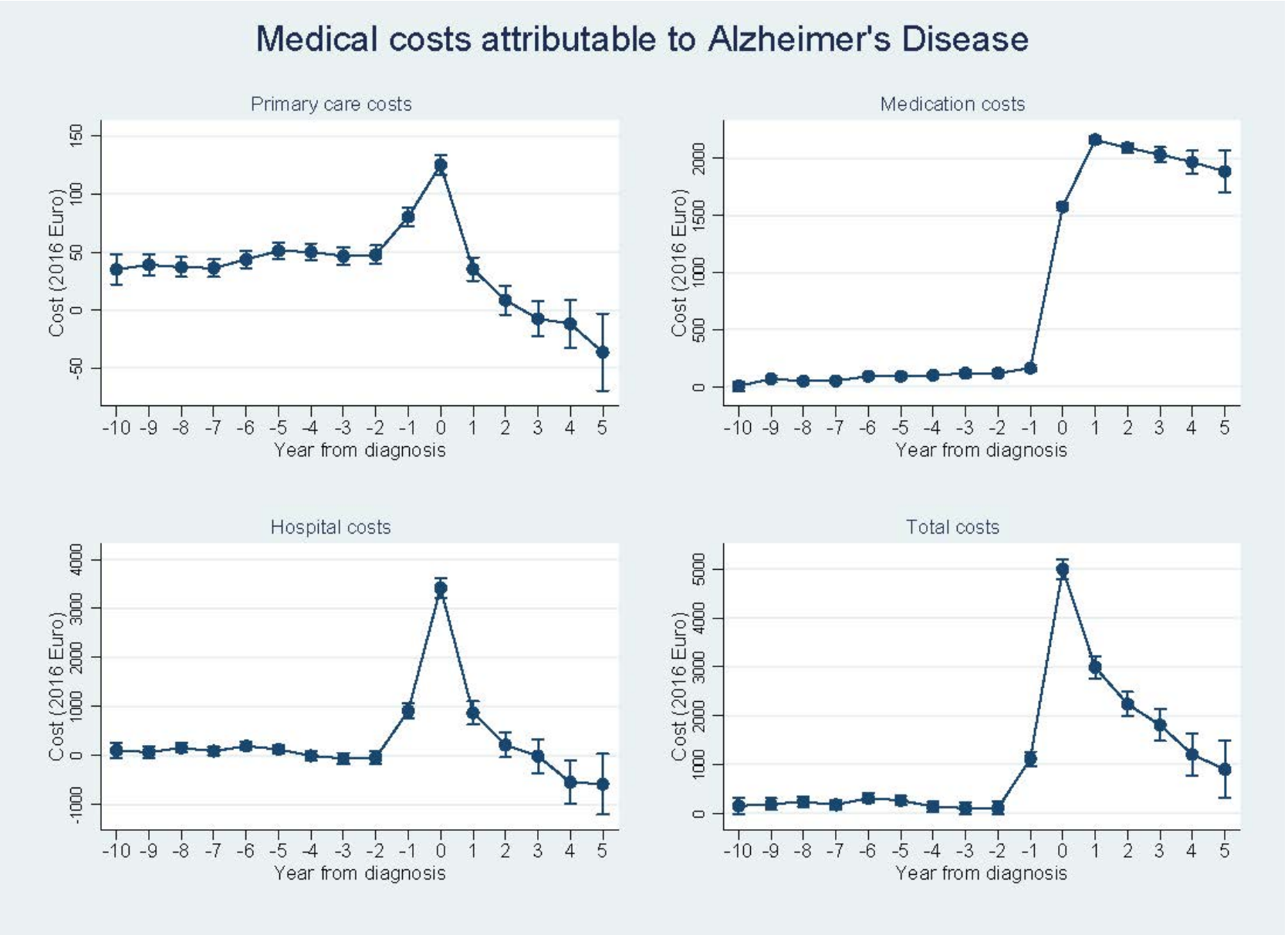
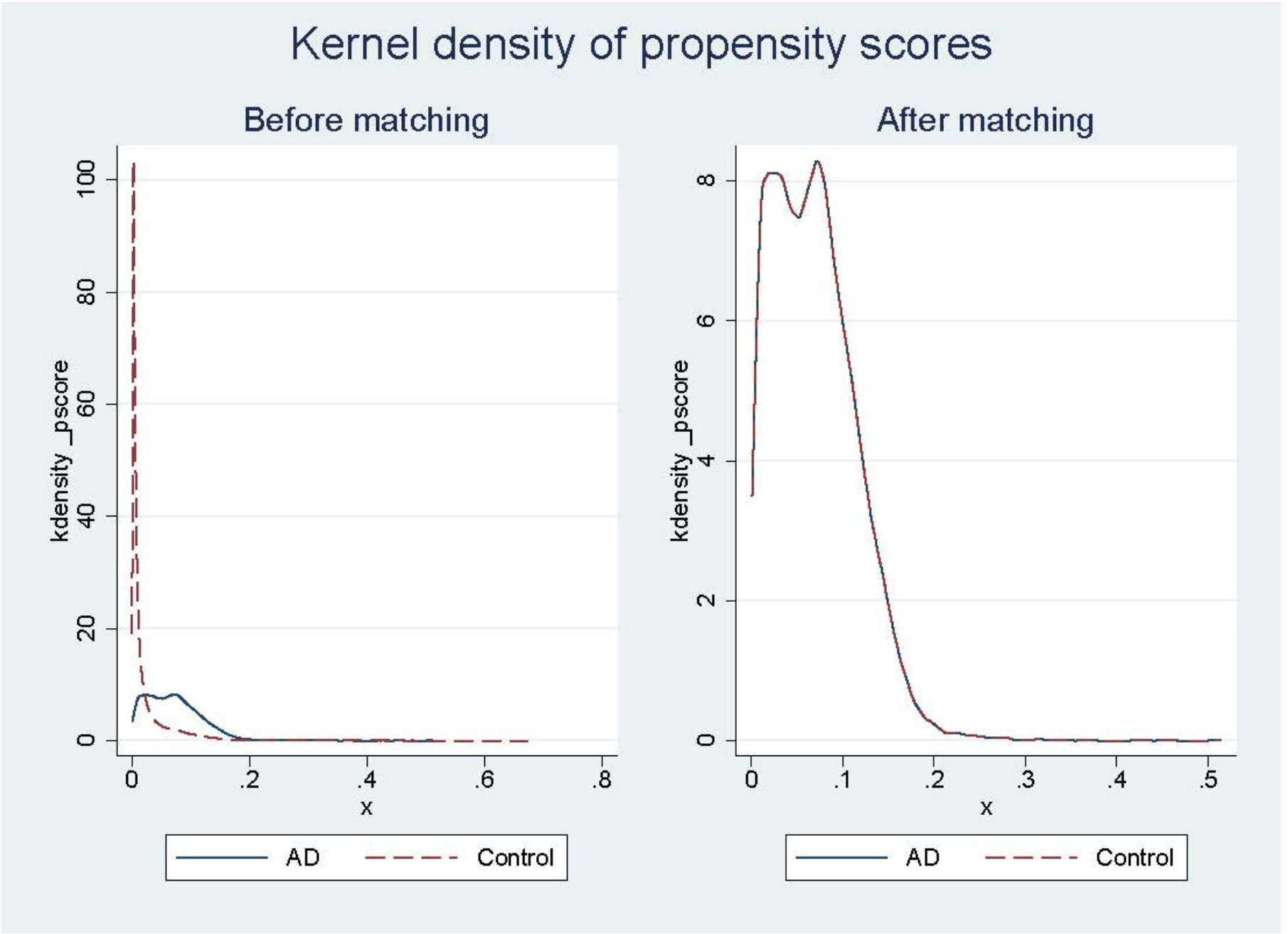
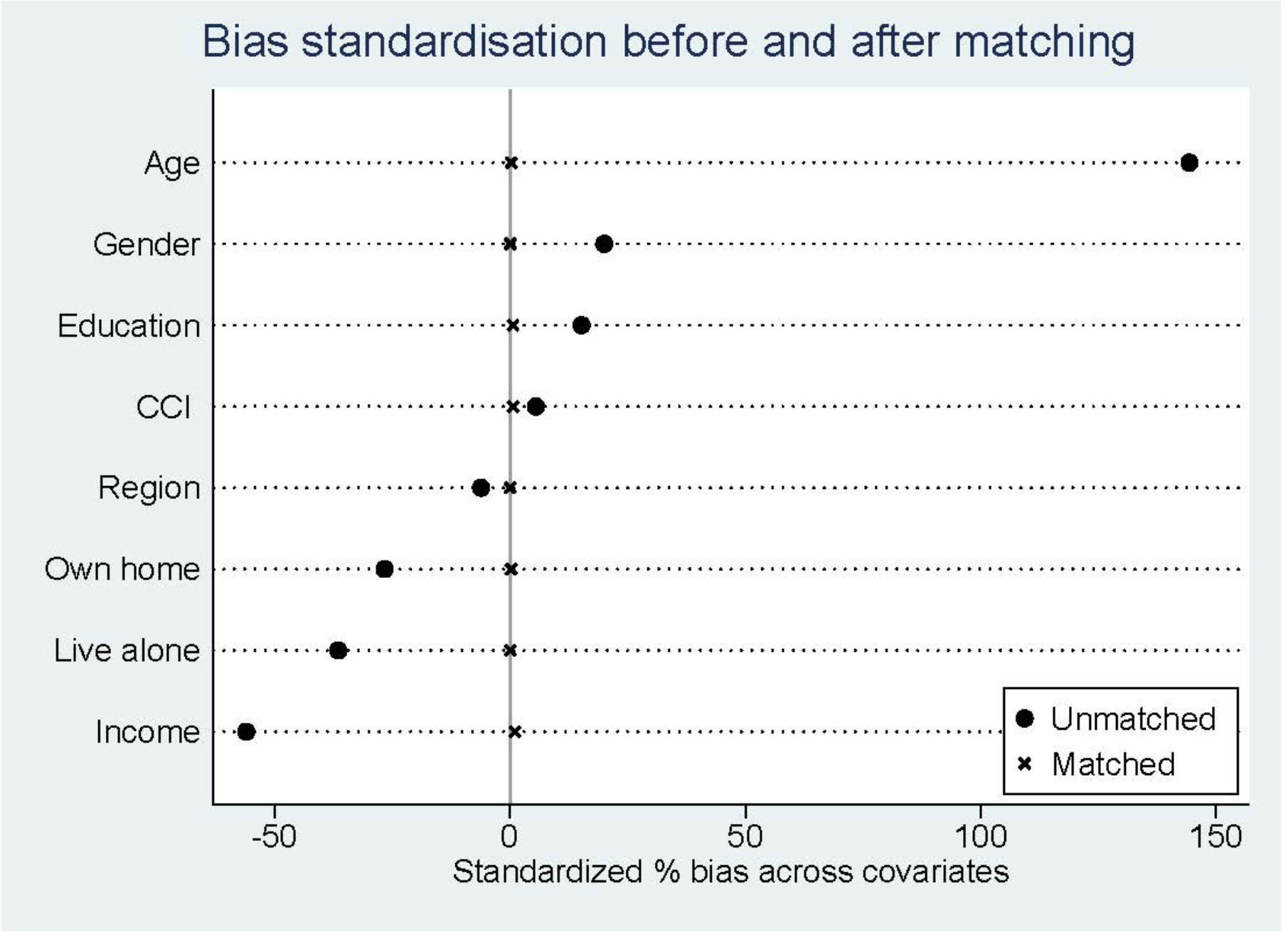


Figure 3 GEE-estimated medical costs attributable to Alzheimer's Disease over 16 years of observation



Supplementary Figure 1: Kernel density of propensity scores for AD and Control groups before and after matching

Supplementary Figure 2: Quantile plot of propensity scores for AD and Control groups before and after matching.



Supplementary Figure 3: Standardised percentage of bias in match and unmatched cohorts.

Supplementary Table 1: Mean primary, medication, hospital and total costs by year from diagnosis.

			Year from diagnosis															
			-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5
Primary	Control	mean	277	287	304	322	336	348	372	394	412	435	449	459	473	479	485	501
		95% CI	(268-286)	(280-293)	(299-310)	(316-327)	(331-341)	(344-353)	(367-377)	(389-399)	(407-418)	(429-440)	(443-455)	(452-466)	(465-481)	(470-488)	(473-496)	(483-519)
		no	5,093	10,032	14,233	18,336	22,886	26,946	26,888	26,698	26,294	25,600	24,648	19,468	14,569	10,374	6,631	2,976
	AD	mean	311	328	343	359	380	399	422	440	460	513	568	490	477	468	468	462
		95% CI	(302-321)	(321-335)	(336-349)	(353-365)	(374-385)	(394-404)	(416-427)	(434-446)	(454-466)	(507-519)	(561-574)	(483-498)	(468-486)	(457-480)	(452-484)	(436-489)
		no	5,093	10,032	14,233	18,336	22,886	26,951	26,951	26,951	26,950	26,949	26,938	20,403	13,931	8,968	5,008	1,964
Medication	Control	mean	669	689	738	786	812	839	888	938	968	985	993	992	992	983	954	953
		95% CI	(643-694)	(671-708)	(722-755)	(771-801)	(798-826)	(826-851)	(875-902)	(924-952)	(954-982)	(970-999)	(977-1009)	(974-1009)	(974-1011)	(962-1004)	(928-980)	(916-991)
		no	5,093	10,032	14,233	18,336	22,886	26,946	26,873	26,674	26,247	25,525	24,547	19,350	14,449	10,286	6,558	2,934
	AD	mean	672	755	782	832	897	925	979	1,047	1,074	1,131	2,466	3,012	2,949	2,884	2,791	2,729
		95% CI	(641-702)	(732-778)	(763-801)	(813-850)	(880-913)	(909-940)	(963-996)	(1014-1081)	(1055-1093)	(1110-1152)	(2441-2492)	(2984-3039)	(2913-2984)	(2830-2938)	(2705-2878)	(2570-2888)
		no	5,093	10,032	14,233	18,336	22,886	26,951	26,951	26,951	26,950	26,948	26,808	20,151	13,739	8,761	4,850	1,899
Hospital	Control	mean	1,100	1,220	1,268	1,475	1,553	1,690	2,016	2,292	2,691	2,980	3,524	3,766	3,918	4,098	4,297	4,569
		95% CI	(993-1208)	(1133-1308)	(1195-1340)	(1405-1544)	(1486-1619)	(1625-1755)	(1940-2093)	(2212-2372)	(2603-2779)	(2887-3074)	(3321-3728)	(3514-4018)	(3660-4177)	(3766-4430)	(3766-4827)	(4231-4907)
		no	5,093	10,032	14,233	18,336	22,886	26,939	26,856	26,637	26,142	25,428	24,389	19,213	14,312	10,173	6,481	2,900
	AD	mean	1,227	1,311	1,371	1,494	1,625	1,698	1,861	2,119	2,440	3,629	6,413	4,339	3,921	3,844	3,586	3,723
		95% CI	(1094-1360)	(1215-1408)	(1298-1444)	(1425-1562)	(1562-1687)	(1638-1759)	(1799-1922)	(2053-2186)	(2364-2516)	(3535-3724)	(6287-6539)	(4224-4454)	(3793-4050)	(3669-4019)	(3378-3793)	(3371-4076)
		no	5,093	10,032	14,233	18,336	22,886	26,951	26,951	26,951	26,949	26,947	26,847	19,923	13,396	8,349	4,587	1,767
Total	Control	mean	2,046	2,196	2,311	2,583	2,700	2,876	3,273	3,617	4,051	4,374	4,919	5,153	5,297	5,459	5,617	5,883
		95% CI	(1928-2164)	(2103-2290)	(2232-2389)	(2507-2658)	(2629-2772)	(2807-2946)	(3192-3354)	(3532-3702)	(3959-4144)	(4275-4472)	(4715-5123)	(4902-5404)	(5040-5555)	(5131-5788)	(5096-6139)	(5542-6225)
		no	5,093	10,032	14,233	18,336	22,886	26,950	26,892	26,705	26,308	25,619	24,680	19,499	14,594	10,399	6,643	2,981
	AD	mean	2,210	2,394	2,495	2,684	2,902	3,022	3,262	3,607	3,974	5,273	9,411	7,688	7,140	6,848	6,438	6,428
		95% CI	(2068-2352)	(2290-2498)	(2415-2575)	(2609-2760)	(2832-2971)	(2956-3088)	(3194-3330)	(3528-3686)	(3891-4056)	(5171-5374)	(9280-9541)	(7569-7807)	(7006-7275)	(6669-7026)	(6216-6659)	(6052-6804)
		no	5,093	10,032	14,233	18,336	22,886	26,951	26,951	26,951	26,950	26,949	26,945	20,439	13,962	8,990	5,022	1,971

Note: Costs are in 2016 Euro
CI: confidence intervals

Supplementary Table 2: Additional medical costs attributable to Alzheimer's disease: model estimated difference between AD and Control costs by year from diagnosis

Year	Primary Costs			Medication Costs			Hospital Costs			Total costs		
	2016 €	SE	95% CI	2016 €	SE	95% CI	2016 €	SE	95% CI	2016 €	SE	95% CI
-10	35***	6.5	(22 - 48)	6	20.4	(-34 to 46)	105	79.9	(-52 to 262)	155	84.0	(-9 to 320)
-9	39***	4.7	(30 - 48)	69***	15.0	(40 - 98)	69	57.2	(-43 to 181)	189***	61.5	(68 - 309)
-8	37***	4.4	(28 - 46)	51***	12.7	(26 - 76)	157***	48.4	(62 - 252)	239***	51.8	(138 - 340)
-7	36***	3.9	(29 - 44)	52***	11.8	(29 - 75)	90**	45.7	(1 - 180)	175***	48.9	(79 - 271)
-6	44***	3.7	(36 - 51)	93***	10.7	(72 - 114)	193***	43.4	(108 - 278)	313***	46.3	(222 - 404)
-5	51***	3.6	(44 - 58)	95***	10.1	(75 - 114)	128***	44.3	(41 - 215)	267***	46.3	(176 - 358)
-4	50***	3.8	(43 - 57)	101***	10.8	(80 - 122)	-4	51.1	(-104 to 96)	137***	52.6	(34 - 240)
-3	46***	3.9	(39 - 54)	118***	14.4	(90 - 146)	-59	56.8	(-170 to 52)	108	58.6	(-7 to 223)
-2	48***	4.1	(40 - 56)	119***	12.0	(95 - 142)	-44	65.2	(-172 to 84)	109	65.2	(-19 to 237)
-1	80***	4.2	(72 - 88)	164***	13.4	(137 - 190)	911***	76.3	(762 - 1061)	1114***	75.6	(966 - 1262)
0	125***	4.5	(116 - 134)	1577***	16.6	(1544 - 1609)	3417***	105.5	(3210 - 3623)	4996***	103.0	(4794 - 5198)
1	35***	5.1	(25 - 45)	2161***	17.7	(2127 - 2196)	871***	119.1	(638 - 1105)	2992***	114.9	(2767 - 3217)
2	9	6.3	(-4 to 21)	2091***	22.0	(2048 - 2134)	217	128.9	(-36 to 469)	2237***	126.1	(1990 - 2484)
3	-7	7.6	(-22 to 7)	2032***	33.1	(1967 - 2097)	-10	175.2	(-354 to 333)	1808***	167.4	(1480 - 2136)
4	-12	10.6	(-32 to 9)	1966***	50.9	(1867 - 2066)	-544**	223.0	(-981 to -107)	1206***	220.2	(774 - 1637)
5	-36**	16.9	(-69 to -3)	1884***	91.7	(1705 - 2064)	-581	314.9	(-1198 to 36)	902***	299.4	(316 - 1489)

CI: confidence intervals; SE: standard error; Year: year from diagnosis
***** p<0.01, ** p<0.05**