Risk factors for incidence of dementia in primary care settings

by

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ABSTRACT

Dementia is a long-term, chronic condition caused by a progressing physical damage in the brain. Evidence suggests that cardiovascular disease risk factors may contribute to the onset of dementia; however, the current literature on this association is inconsistent. To my knowledge, no study that has explored the occurrence of cardiovascular risk factors prior to a diagnosis of dementia using national primary care data in North America.

I used electronic medical records from the Canadian Primary Care Sentinel Surveillance Network to create a Canadian cohort to conduct a retrospective analysis to (1) determine the number of incident diagnoses of dementia among community-dwelling seniors; (2) describe demographic and clinical characteristics of people living with dementia in community; (3) describe current situation of modifiable cardiovascular risk factors being managed in primary care; and (4) compare the risk of developing dementia in seniors (aged 65 and older) with and without modifiable cardiovascular risk factors.

The cohort identified 39,066 patients who were 65 or older and did not have a dementia diagnosis in or before 2009. During nine years of follow-up, 4,935 individuals developed dementia. Overall, the number of patients with dementia or heart disease risk factors increased slightly but steadily over the nine-year follow-up period.

Age were associated with an increase in risk for incidence of dementia in all ages, HR = 1.13 (95% CI, 1.12-1.14) and 1.05 (95% CI, 1.04-1.06), respectively, for people aged 65-79 and people aged 80 and over. History of depression also

increase dementia risk by 38% and 34%. There was association with social index, smoking history, osteoarthritis and diabetes mellitus in people aged 65 to 79 but not in those aged 80 and older. Sex, hypertension, obesity and dyslipidemia diagnosed and managed in primary care did not significantly predict dementia onset. Antihypertensive and statin use was not associated with risk of diagnosis. People with dementia are more likely to weigh less and to lose more weight than those who have not been diagnosed with the disease.

Diabetes mellitus and underweight increase the risk of dementia developing. Monitoring BMI and managing change in BMI in primary care may help to diagnose dementia earlier which might be a good reference for family medicine and public health to plan an advanced treatment strategy for people in need. Routine screening for cognitive decline on older adults with those two conditions might benefit to provide early diagnosis and support for those in needs.

PREFACE

This thesis is an original work by Nguyen Quynh Anh Pham. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Risk factors for incidence of dementia: a retrospective cohort”, No. Pro00083659, 2018.07.17. No part of this thesis has been previously published though chapter two, three, and four are written in academic journal format in order to prepare for publication.

Dedicated to

My Husband Nguyen Thanh Dien,

My Daughters Nguyen Pham Ha An and Nguyen Pham An Di,

My Sister Pham Nguyen Quynh Nhu,

and my dear Grandmother Nguyen Thi Loc.

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LIST OF ABBREVIATIONS

AB	Alberta
ATC	Anatomical Therapeutic Chemical
BC	British Columbia
CI	Confidence Interval
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
CVD	Cardiovascular Disease
EMR	Electronic Medical Records
GLM	Generalized Linear Model
HR	Hazard Ratio
ICD	International Classification of Disease
MB	Manitoba
MI	Multiple Imputation
NB	New Brunswick
NL	Newfoundland and Labrador
NS	Nova Scotia
NT	Northwest Territories
ON	Ontario
OR	Odds Ratio
PE	Prince Edward Island
QC	Quebec
SAPCReN	Southern Alberta Primary Care Research Network
SD	Standard Deviation
SK	Saskatchewan

CHAPTER 1. INTRODUCTION

1.1 The aging Canadian population

The Canadian population is aging at a faster rate than it has ever done before (1). From 1992 to 2012, the median age of Canadians increased from 33.6 years to 40.0 years (2). By 2011, average life expectancy in Canada had increased, by roughly 15 years, to approximately 82 years of age (3). This increase in longevity is a considerable achievement; however, the higher proportion of older people in the population brings new challenges that require Canada to make changes in health-related financial distribution, the delivery of healthcare at both provider and system level, and public infrastructure (1).

1.2 Dementia overview

The dementias are long-term, chronic cognitive conditions resulting in loss of memory, reasoning ability, and changes in personality (4). According to International Statistical Classification of Diseases and Related Health Problems (ICD)-10 coding, dementia includes, but is not limited to, a decline in functional memory, new information learning ability, and at least one additional domain of cognitive deficit (5). While cognitive decline may often be seen as being a normal part of aging, dementia is a chronic degenerative condition caused by progressive physical damage to the brain (6). The dementias are normally grouped according to the underlying pathological condition which impairs brain function. Globally, Alzheimer's disease is the most common sub-type, accounting for about two-thirds of the total number of people diagnosed with dementia. Patients with Alzheimer’s disease lose synaptic connections due to tangles of fibres that cause death of brain cells. When the damage is more severe than the brain's self-repair capability, symptoms of Alzheimer's disease become noticeable (7). The second most common sub-type of dementia is vascular dementia, which is caused by a failure of blood supply to the brain. Normally, vascular dementia comes after a stroke (stroke-related dementia) which may be not clinically apparent, or a transient

ischemic attack (small vessel disease-related dementia) (7) and shares underlying risk factors with cardiovascular diseases.

1.3 Diagnosis of dementia

Diagnosis of dementia is complicated as it requires a comprehensive evaluation and evidence of cognitive decline over time, and there is no diagnostic test for the condition (5, 8). Guidelines on the diagnosis of dementia are now leaning more towards finding a right time to make the diagnosis, which is when people with dementia and/or their caregivers start to need support (8, 9). Symptoms and signs of early dementia are vague, non-specific and rarely recorded by physicians or reported by patients; they are more likely to be noticed by a close family member (8). The Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia recommended a six-step process to diagnose dementia: (1) personal and family medical history, (2) family member or caregiver interview, (3) physical examination, (4) cognitive tests, (5) laboratory tests, and (6) brain imaging (10).
There are a number of cognitive tests used to assess dementia, each having advantages and disadvantages. Brief cognitive tests are often conducted by general practitioners, including the Mini-Mental State Examination (MMSE) (11), the clock-drawing test (12), the Montréal Cognitive Assessment (13), DemTect (14), the 7-Minute Screen (15), the General Practitioner Assessment of Cognition (16), or the Behavioural Neurology Assessment short form (17). Each requires roughly five to ten minutes to complete; evidence from research suggests that the Dementia Rating Scale (18), the Clock-Drawing Test (12), and the Mini-Mental Status Examination (11) are more comprehensive than the others (19). However, Canadian guidelines suggest that a physician should choose a test based solely on their experience and preference (10).

Only an autopsy can confirm an Alzheimer's disease case (10). Brain imaging technology such as computed tomography and magnetic resonance imaging may be used for differential diagnostic purposes, for example to exclude brain tumours,

but they can neither exclude nor confirm the diagnosis of dementia (20). Other tests such as electrocardiography or blood tests are used to define risk factors and/or treatment plans (20).

The Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia in 2012 (21) recommended that clinical diagnosis guidelines remained as in the previous version (10). Briefly, core clinical criteria for diagnosing all causes of dementia include impairment in the ability to maintain daily activities and previous level of functioning, and the presence of cognitive impairment in at least two major domains which cannot be attributed to delirium or other mental disorders (22). In general, even a simple diagnosis of dementia is not straightforward and attempts to revise these diagnostic criteria have been unsuccessful. Although there is increased awareness of dementia among family physicians from Canada and beyond (23), there have been no major differences in the diagnosis criteria of dementia between 2008 and 2017.

1.4 Risk factors for incidence of dementia

A comprehensive search on the *PubMed* database in December 2018 for papers on risk factors for the development of dementia was performed in six steps using the following terms:

1. (dement* or Alzheim*).m_titl.
2. (risk factor* or predictor*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 AND 2 AND (exp Hypertension/ or exp Blood Pressure/)
4. 1 AND 2 AND (exp Diabetes Mellitus, Type 2/ or exp Blood Glucose/ or exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus/)
5. 1 AND 2 AND (exp Dyslipidemias/)

6. 1 AND 2 AND (exp Body Weight/ or exp Weight Gain/ or exp Weight Loss/)

The search yielded 1,278 studies in total from steps 4, 5 and 6. All titles found were first examined to eliminate irrelevant (For instance, a study on Apolipoprotein E4 from the dyslipidemia search or one on insulin resistance from the diabetes search) or duplicate entries. After reviewing titles, 874 studies were excluded. The 404 abstracts of those that remained were then reviewed to ensure:

(1) studies have incorporated a follow-up cohort (longitudinal design, including cohort and case-control studies);
(2) the primary outcome in the analysis used is incident dementia (could be all-type dementia, vascular dementia, and/or Alzheimer's disease.);
(3) authors have clearly specified predictors of dementia, including at least one of blood pressure or hypertension, blood glucose or diabetes mellitus, serum cholesterol or hyperlipidemia or dyslipidemia, and body mass index or obesity;
(4) studies were conducted at population level;
(5) studies on men or women alone were still eligible for inclusion;
(6) studies were written in English, Chinese, or Vietnamese; and
(7) there was no specific eligibility restriction for time or place of publication.

Three-hundred-and-four studies were excluded for having at least one of the six reasons listed below (references given as examples):

(1) being cross-sectional studies not accounting for time and sequencing between predictors and outcome (24, 25);
(2) prevalent dementia was not ruled out; studies did not clearly indicate strategies to exclude pre-existing dementia cases at baseline (26-28);
(3) people living in long-term care institutions or hospital inpatients were included (29);
(4) 'probable dementia' and/or mild cognitive impairment were studied (30-32);
(5) the association between predictors and dementia was combined into a mutual scale or risk score rather than being investigated separately (33); or

(6) primary predictors did not include one of the four listed above, or included them but changes or variations in them were evaluated rather than the actual number (34).

Full-texts of the remaining 100 abstracts were read and critically assessed using the Critical Appraisal Skills Programme (CASP) checklists for systematic review (35), cohort study (36), and case control study (37). Each checklist contains sets of questions to support the decision of whether a study is valid and its results are helpful contributions to research in Canada. All of them ask reviewers to carefully consider whether the study of interest has appropriate research question(s), a good study design including methods for recruiting participants/articles, minimizing bias and confounding factors, and its representativeness and precision. Main reasons for excluding studies in this critical step were not having a clear research message, not including a clear method section (Unable to duplicate using described methods), studies in a specific sub-group of people that could not represent a general population (For instance, World War II veterans (38)), or comorbidities and confounding factors not appropriately assessed.

A total of seventy-two studies were included in my full literature review, including six additional papers identified from reference lists of included papers using the snowball method. A meta-analysis was not conducted because it was clear that homogeneity was not present since examination revealed a wide range of variation in participant inclusion criteria, risk factor status identification criteria, dementia diagnosis criteria, and length of follow-up time.

Figure 1-1 and 1-2 show a flow chart of the searching and identifying paper procedure. Numbers provided in this flowchart may not add up to seventy-two papers as there are studies that cover two or more risk factors and are counted more than once.

Figure 1-1. Flowchart of paper selection and inclusion

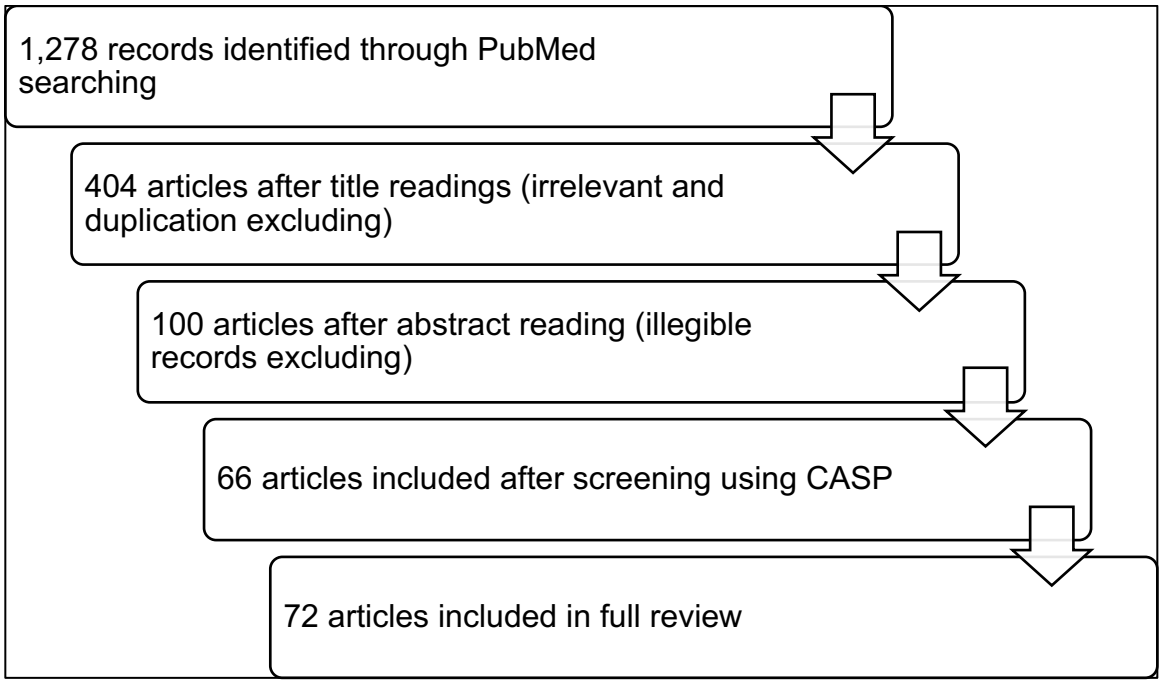
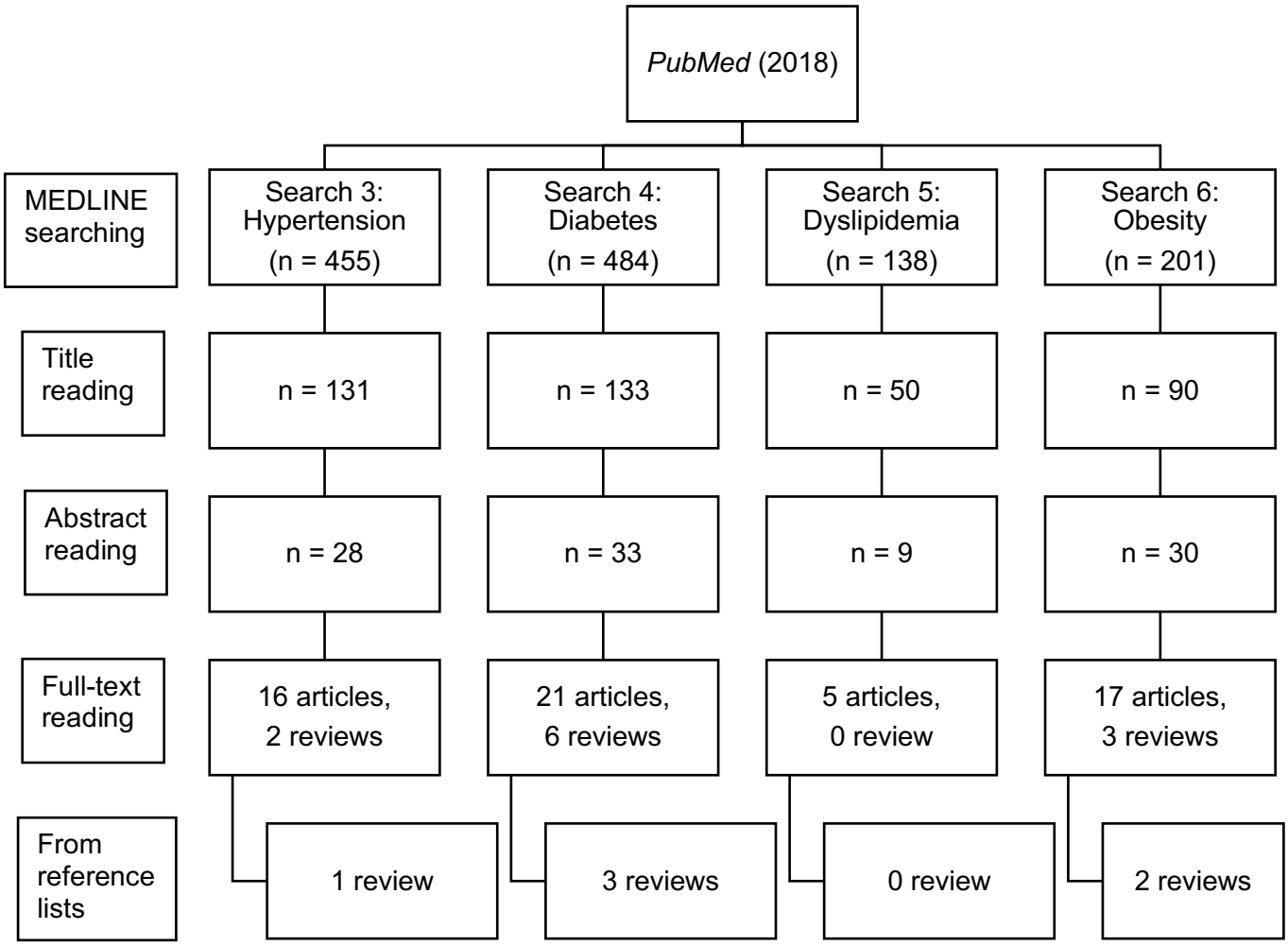


Figure 1-2. Flowchart of paper selection and inclusion, breaking down by risk factors



A summary of the seventy-two studies included in the detailed literature review is presented in appendix I. In general, the evidence for association between cardiovascular disease risk factors and dementia is clearer and stronger for mid-life risk factors, especially hypertension and diabetes, but not for other associations which were examined. Table 1-1 presents the number of studies those support possible associations their directions. I assumed that sufficient evidence for a specific proposed association should have fairly high consistency between at least three studies.

Table 1-1 Quantifying the association between four cardiovascular disease risk factors and dementia onset capturing in current literature

	Number of included studies	Association (number of evidence)	Consistency across evidence	Conclusion on the association
Mid-life				
Hypertension	7	Increase (3) Decrease (1) No association (3)	Moderate	Unclear
Diabetes	3	Increase (2) No association (1)	High	Increase with insufficient evidence
Obesity	10	Increase (4) Decrease (2) No association (4)	Moderate	Unclear
Dyslipidemia	2	Increase (2)	High	Increase with insufficient evidence
Late life				
Hypertension	14	Increase (6) Decrease (1) No association (7)	Moderate	Unclear
Diabetes	20	Increase (16) No association (4)	High	Increase with strong evidence
Obesity	12	Decrease (6) No association (6)	Moderate	Unclear
Dyslipidemia	6	Decrease (1) No association (5)	High	No association with strong evidence

Globally, the relationship between risk factors for heart disease and the incidence of dementia has not been extensively studied. With the exception of a project in Nigeria (39), all included studies were conducted in high-income countries, including the Adult Changes in Thought (ACT) (40), the Rush Memory and Aging Study (MAP), the Kungsholmen Project (41), the Cardiovascular Health Study (42), the Framingham Study (43), the Honolulu-Asia Aging Study (HAAS) (44), the Cache County study (45), the Canadian Study of Health and Aging (46), the Swedish Twin Registry (47), the Rotterdam Study (48), the Italian Longitudinal Study on Aging (49), and the Hisayama Study (50). All but one included retrospective secondary data collected a few decades previously to study other chronic conditions, such as heart disease. For example, the Honolulu-Asia Aging Study obtained participant data from survivors of the Honolulu Heart Program, which was a population-based prospective cohort study of heart disease and stroke, started in 1965 (51). There are several advantages in the use of previously collected data. Firstly, mid-life risk factor information is commonly available, and studying a causal pathway for dementia is potentially feasible. Secondly, previously developed databases are a good source of information to calculate a hazard ratio or time-to-event (for instance dementia diagnosis) in the target population.

In these studies, the age of included participants ranged from the early 30s (52-54) to those over 50y (55-58). These studies had a vital advantage as their aetiologic follow-up time was long, from ten to over 30 years. They also provide a full picture of health conditions of participants remaining in the final cohort. However, one should be aware of potential misclassification bias since data were collected a long time ago, when health care equipment, staff, and other resources may have been different compared to today. Furthermore, diagnostic guidelines and case definitions may have been modified, which might create systematic bias (59). Also, missing data due to loss to follow-up were relatively common. On average, the number of study participants ranged from about two hundred to over eight thousand, while losses to follow-up were between 20-30%. For example, in

the Israeli Ischemic Heart Disease study conducted in Jewish male civil and municipal employees the original cohort was followed-up for more than 30 years, and resulted in missing data for over 43% (60); the Kaiser studies started with over 20 000 observations when subjects were 40 to 55 years old and ended with a cohort of approximately 10,000 forty years later, losing 51% of their participants (61, 62).

My search identified five studies that recruited subjects from national databases and included very large samples. Taiwanese research groups contributed three papers, which analysed the National Health Insurance Research Database of Taiwan, and included over 40 000, 1 000 000 and 200 000 patients respectively (56, 63, 64). The Health Improvement Network (THIN) study in the UK included almost 1 000 000 patients (65), whereas a Korean project included over 800 000 customers of the Korean National Health Insurance Corporation (27). A vital advantage of these projects is that missing data were very rare, they also were able to extract data from other sources via linkage. Loss to follow-up was as low as 0 to 2%.

Except for these five papers using large national retrospective data registries, most studies did not sufficiently describe their target population. Some studies specifically targeted one sex, such as the Honolulu-Asia Aging Study of Japanese-American men, while a longitudinal study in Gothenburg, Sweden, studied only women (66). Other studies limited their target sampling to more closely defined groups such as male veterans (60), businessmen (54), or Catholic clergy (67). A small number of studies also included institutionalised patients (68, 69). Note that all studies based in the United States recruited patients covered by Medicare, a governmental health care insurance which mostly includes people older than 65 years and younger low-income people with some specific health conditions (70). Research based on the older groups using Medicare data is more reliable and generalizable, whereas younger Medicare patients might be more likely to have

severe health-related issues and are not representative of the general American population.

1.4.1. Blood pressure level and hypertension

The risk factor for dementia most commonly assessed is blood pressure. Up to December 2017, there were thirty-two papers from different population-based cohorts that assessed an association between blood or pulse pressure and the incidence of dementia. However, even though a majority of publications found that hypertension is a potential risk factor for dementia onset, there also are papers that report decreases in blood pressure among people with dementia and those who have just been diagnosed with the condition, though no reasonable biological explanation for the latter has been described and the association may not be causal. Hypertensive medication prescribing appears not to change the association between blood pressure and dementia incidence. All of the published analyses do not control for the impact of cardiovascular disease and common comorbidity (such as cancer or an end-of-life event) which may lead to lower blood pressure among older adults.

Among papers whose findings showed an increment in risk of dementia related to hypertension the range of increments was broad, and there was a mixture of statistically significant and non-significant results. For instance, 10-mmHg increments in mid-life systolic blood pressure were associated with increased risk of dementia incidence of 9% (39), 23% (71), and 33% (72), whereas a 10mmHg increase in diastolic blood pressure and pulse pressure was also associated with an increment of 10% and 22% in the risk of dementia (39). In patients with very high systolic blood pressure (> 180 mmHg), the risk of dementia and Alzheimer's disease increased by 60% and 50%, respectively (73). Treating blood pressure as a binomial variable, the Honolulu-Asia Aging Study suggested an increase of between 47% and 84% in the risk for incidence of dementia among hypertensive men older than 70 years (74). Other studies agreed, reporting increases of 50%

and 120% in the odds of developing dementia among patients with higher systolic blood pressure (26, 39). Mid-life hypertension increased the risk of vascular dementia five-fold and doubled the risk of all-cause dementia, regardless of late-life blood pressure levels (75). It has been suggested that people with hypertension before 65 years of age were more likely to have dementia later in life, an association which was more pronounced in patients with vascular dementia than with Alzheimer's disease (26, 27). Regardless of whether patients were prescribed hypertensive medications or not, the risk of developing dementia was stronger among patients with an index hypertension diagnosis before the age of 50 years (76, 77). Among people with both heart disease and hypertension, the odds of developing dementia were statistically significantly 3.3 (95% CI [1.7-6.6]) times the odds among those who were free from heart disease and hypertension (78). The co-existence of hypertension and diabetes also increased the odds by 6.2 (95% CI [2.9-13.5]) times (78).

However, in some studies, the association was not statistically meaningful, and this was true for both vascular dementia and Alzheimer's disease patient groups (48, 78-81). Among uncontrolled-hypertensive patients, systolic blood pressure was not a statistically significant predictor either (74, 80). On the other hand, some studies have also reported that hypertension significantly decreases the risk of dementia onset by from 9% to 138% (34, 71, 77, 82).

For hypotension, the risk of developing dementia and Alzheimer's disease among people with very low diastolic blood pressure (less than 65 mmHg) was 54% (dementia) and 70% (Alzheimer's) higher than that risk among people with normal blood pressure, respectively (74). Blood pressure is more likely to fall in one's later years, specifically a few years before dementia diagnosis (82, 83). Among people over the age of 85, low blood pressure (diastolic blood pressure < 70 mmHg) increased the risk of Alzheimer's disease by 91% (HR=1.91) (71); whereas hypertension reduced the risk for dementia by 24% among people older than 50

years old (76). A birth cohort study suggested hypertension reduced the risk between 45-53% depending on the number of confounders being adjusted for (84).

Further, the effect on incident dementia caused from varying blood pressure levels over time is also inconsistent. A French study suggested the bigger the difference of blood pressure between visits, the higher the risk of dementia onset (85); however, the Honolulu-Asia Aging Study in Japanese-American men found that change in blood pressure levels over time was not associated with risk (77).

In general, it would appear that hypertension may increase the risk of incident dementia but hypotension may also increase the risk. The evidence supporting the hypothesis that hypertension increases the risk of developing dementia, especially dementia other than vascular dementia, is inconsistent. Previous literature reviews which confidently suggest that 'maintaining good blood pressure' can help reduce the risk of dementia later in life (86), or that by the elimination of all cardiovascular disease risk factors the proportion of demented cases could decrease by about 25-30% (57), appears to have strong supportive evidence. Though the relationship between blood pressure and subsequent dementia remains unconfirmed as comparable studies independently conclude that both high and low blood pressure significantly and non-significantly increase the risk of dementia onset.

1.4.2. Blood glucose level and diabetes mellitus

The evidence for an increased risk of incident dementia in patients with diabetes is more consistent than in hypertension. Most papers support the hypothesis of an increased risk of incident dementia in the elderly with diabetes. One project that studied impaired glucose tolerance also suggested an increase in risk (87).

The reported association was strongest when the health outcome was vascular dementia. Comparing people with and without diabetes, the relative risk of developing vascular dementia ranged from 1.03 to 2.77 (48, 88, 89).

For Alzheimer's disease, the risk of developing dementia statistically significantly increased by 2.0-3.8 times (48, 68, 80, 90). However, some studies found that the statistically significant association was lost after adjusting for potential confounders, including age, sex, and educational level (80, 88), though the 95% confidence interval was narrow, from slightly lower than 0 to around 2. A pooled effect size in a meta-analysis showed that the risk of developing the disease in people with diabetes was 1.54 times the risk in people without diabetes (91).

For all types of dementia, a diagnosis of diabetes preceding the baseline assessment was associated with an increased risk of incident dementia diagnosis of 46-73% (60, 61, 63, 64, 92-95). This trend held for both mid and late-life diabetes (96). However, the increased risk reduced in association with increasing age, involving 33% of patients aged 60-79 years and 20% of patients aged 80 to 95 years (65). The risk was highest among women with diabetes diagnosed earlier than 65 years old (27). Impaired glucose tolerance also increased the risk by 61%. In adult patients aged 30 years or older, the risk for all types of dementia in those who both had diabetes and elevated systolic blood pressure was quadrupled compared to those who did not have the two conditions (87).

On the other hand, when studies analysed data from patients with diabetes in a multivariable analysis with other potential risk factors, there was a weaker or non-significant association between diabetes and incident dementia (45, 57, 62). Additionally, a few studies suggested that diabetes could be protective against dementia via insulin resistance (97). However, evidence for this hypothesis is limited and remains uncertain (98).

1.4.3. Blood lipid levels and dyslipidemia

Generally, studies have found that high blood cholesterol, high triglycerides, high low-density lipoprotein – cholesterol (LDL-C), and/or low high-density lipoprotein –

cholesterol (HDL-C) increase the risk of dementia incidence. Though it should be noted that among patients aged 75 years and older, a contradictory situation was observed.

In males, low HDL-C increased the risk by 45%; for those without vascular pathologies, low HDL-C increased the risk by 54%, and high triglycerides increased the risk by 56% (99). Increasing total cholesterol by 0.7 mmol/l also increased the risk of Alzheimer's disease by 60% to 103% (54). Elevated levels of total cholesterol among 60 year olds were associated with mild cognitive impairment and Alzheimer's disease 14 years later: a decrease of total cholesterol in the 4 years before Alzheimer's disease diagnosis was a marker of ongoing disease (100).

When analysing blood lipids as a continuous variable, for each one-mmol/l increase in total cholesterol the risk of dementia increased by 20%; while each one-mmol/l increase in LDL-C increased the risk of all dementias, including Alzheimer's disease, by 6-13% (54). In general, there was a pattern observed for the different lipid fractions, where higher baseline LDL-C and total cholesterol were associated with Alzheimer's disease, while higher baseline triglycerides were associated with vascular or mixed dementia (101).

However, findings were different among the oldest group. A one-mmol/l increase in serum cholesterol was associated with a decrease in the incidence of dementia by 30-38% (102). Stratifying by sex showed no difference in levels of risk between males and females. Among women, low triglycerides (less than 0.85 mmol/l) decreased the risk of all type dementia and Alzheimer's disease by 30% and 40%, respectively; whereas among men, for every one-mmol/l increase in log transformed triglycerides, the risk of incident dementia reduced by 51% (99).

Other studies, however, found no significant association between the presence of higher total cholesterol and the incidence of Alzheimer's disease or

undifferentiated dementia (45, 102). HDL-C was not associated with risk of any types of dementia (53, 101).

1.4.4. Body mass index, waist-hip ratio, body adiposity and obesity

Currently, the evidence for the association between these factors and incident dementia diagnosis is inconsistent. Being obese and overweight was found to be linked to subsequent development of dementia in several studies. Obese patients (body mass index (BMI) greater than 30) had a 26% to 144% greater risk of dementia than those who have normal BMI (103-105). In one study, every one-unit decrease in BMI was associated with a 3% decrease in risk (66). Beydoun and colleagues followed a cohort in a Baltimore community for twenty years and found that obesity increased the risk for incidence of dementia by 74%, but there was no difference between risks associated with obesity either in middle or late life (105).

For other measurements that relate to body adiposity, a decrease in incident Alzheimer's disease was found among males who had small waist circumference at the age of 30-35 (HR=0.55) (106). But for a one-unit increment in subscapular/triceps skinfold thickness ratio, the risk for incidence of vascular dementia reduced by 2%, and for Alzheimer's disease by 15%, though these findings were not statistically significant with a 95% confidence interval narrowly around one (88).

On the other hand, other some studies reported a different effect of BMI on dementia incidence. For example, a decrease of one unit in BMI in late life increased the risk of dementia (HR= 1.89); while a two unit decrease in BMI increased the risk by 66% (RR=1.66); both estimates were precise with narrow confidence intervals around the point estimates (67, 107). An increment in the risk of Alzheimer's disease was also found in males who increased or decreased their BMI by greater than 9% at any age and in females who had BMI changed less than 10% between 35-45 years old (105). For all types of dementia, risk of disease

incidence among underweight 65+ year olds was 48% higher than the risk among those of normal weight (108). Among white women, for a one-unit increase in BMI at the age of 70 or earlier, the risk of dementia reduced by 5.4% (66). For Alzheimer's disease, males who were underweight in their 30s experienced an increased risk of incident dementia in late adulthood 6.05 times more than those who had a normal weight. The risks of dementia in late life for underweight males at 40 to 45 years old and 45 to 50 years old was11.89 and 11.21, respectively. Though the confidence intervals in these findings were wide, spreading from approximately 2 to 50 (106), indicating a lack of precision in the finding.

1.5 The burden of dementia

As of 2016, worldwide there were 47 million people living with dementia, even though the true number of dementia cases may be much higher since, in high income countries, only 50% of people are diagnosed, and in low-income countries the proportion is even smaller (109). Additionally, not many diagnosed cases receive appropriate treatment (110).

In 2008, Canada had over 480,000 dementia cases, and it is expected that by 2038 in Canada the number of cases will be over 1,125,000 (111). In 2012, among all community-dwelling persons aged over 65, the prevalence was 7.3% (112). Even though patients often first visit family physicians when they notice dementia-related symptoms, diagnosis is more frequently made by specialists (23), which might lead to an underestimation of dementia prevalence using primary care electronic medical records (EMRs).

Dementia is a disease that not only affects the individuals with the condition, but also their families, friends and communities. Often people who live with those with dementia sacrifice their time and resources for most people living with dementia, particularly with more advanced disease, are not capable of maintaining independent living (113). In addition, patients with dementia often have multiple

co-morbidities, which makes it challenging for care providers to devise a comprehensive treatment plan (109), and for caregivers to assist in implementing them (114). When a patient is still living at home, they may need round the clock support in activities of daily living, including basic support such as meals, bathing, or transportation (115). One may also need extra support for safety assurance. At later stages, if a patient has to be accommodated in a long-term care facility, their caregivers still need and usually want to be an active part of a team that provides supportive care for the patient (109). In Canada in 2008, a total of 231 million hours of informal care was spent caring for patients with dementia by their family members, accounting for $4.9 billion in opportunity costs (111). Economically, in 2016 Canada committed a total of $10.4 billion for dementia, including $8 billion in direct and $1.8 billion through indirect costs; this sum is predicted to double by 2030 (116).

1.6 Current gaps in primary care practice-based research

In the last thirty years, dementia has gained the attention of researchers with an increase in the quality and quantity of studies assessing risk factors and identifying areas of preventability (117). However, most existing research focuses on downstream, tertiary prevention, after the disease has already been diagnosed and severely affects patients' daily activities (118).

Studies have shown that people with high risk for cardiovascular disease are also at high risk of dementia though, as discussed above, the relationship between cardiovascular disease risk factors and dementia is not clear (119). It was reported that hypertension, hyperlipidemia, and type-two diabetes were associated with an increase in the incidence of diagnosed dementia (106, 120). Modifiable cardiovascular risk factors (physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes), together with depression, and low educational attainment were found in approximately 33 per cent of patients with Alzheimer's disease (121). Furthermore, researchers have recommended that maintaining

appropriate body weight, blood pressure, blood glucose, and cholesterol levels might be causally linked with decreasing, or delaying the incidence of dementia (122-124). A 10% reduction in hypertension, diabetes, smoking and other risks could reduce the prevalence of dementia by 8.3% (125). A one-year delay in the mean age of dementia onset could lead to a 10% reduction in dementia prevalence by 2050 (115). A recent study in Ontario has shown that the incidence of dementia is declining, along with a declining incidence of stroke, which might further suggest an association between cardiovascular disease risk control and overall health status in the community (126, 127).

1.7 Treatment and prevention plan for dementia

There is no clear evidence of the effect of any medications or therapies that may improve or delay dementia progression. With regard to medications, cholinesterase inhibitors are recommended for mild to moderate dementia, and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine, is recommended for moderate to severe dementia. However, evidence for their effectiveness is not strong, while their associated adverse effects are substantial and frequent (128). Pharmacologically, cholinesterase inhibitors are designed to block the enzyme that breaks down acetylcholine, a neurotransmitter that significantly affects memory (129). Hence, they are claimed to help to delay the development of dementia-related symptoms and prolong the time to continuing care admission (23). Memantine may be combined with cholinesterase inhibitors to improve behavioural and psychological symptoms in dementia (23). For vascular dementia, no specific drug is yet recommended, though evidence suggests that practicing a physically and mentally healthy lifestyle to avoid vascular disease would help to reduce this sub-type of dementia (23). Some activities that may help people to avoid or delay dementia onset include a healthy diet, regular physical activities, an active social life which involves intellectual activity, and head injury prevention (111).

The Alzheimer's Society of Canada proposed a 10-year physical activity program, which encourages dementia-free seniors to increase their levels of physical activity from moderate to high. It is believed that increasing the intensity of physical activity could contribute to a decrement of 4.3% incident cases and 5.1% prevalent ones, thereby reducing health costs by 2.4%, or roughly $5.6 billion (111). The effectiveness of this program is yet to be proven.

1.8 Current policies in dementia diagnosis, treatment, and prevention

The Quality and Outcomes Framework (QOF) – one of the largest payment-for-performance models in the world – was implemented in the UK in 2004 (130). Basically, it is a program to encourage general practitioners (GP) to perform 'good practice' in a number of components, including increasing screening, testing, and diagnosing new cases of a few targeted chronic health conditions by providing extra funding according to performance attainment (130, 131). Findings from evaluations of the effectiveness of the framework which seek to establish a causal relationship between the employment of the framework and performance (132) were inconsistent. Anecdotally, quality of care for domains and health conditions included in the framework impressively improved, such as a slower increase in emergency and hospital admission for all included domains, including care for dementia (132-134). However, in the second year of participation, the improvement in GPs' and nurses' performance remained the same as that achieved in the first year for most indicators, which might be explained by the performance becoming optimized (134). But evidence also found that performance in non-incentivised conditions improved less than among those that were incentivised, and could be even poorer than before the intervention (133, 135), suggesting that some outcomes were beneficial, leading to the suggestion that future practice should aim to improve the QOF rather than to abandon it (135). Another good outcome was that health data input improved in both quality and quantity (135), though its accuracy remained unclear (133).

By 2016, Scotland had ended the program, while England modified it for a number of essential reasons, including inequitable payments between big and small clinics, inconsistent codes for health conditions that may cause patients to disappear from the record, the complication in accurately recording patients with multimorbidities, and, especially, the continually increased workload on GPs (133). The impact of removing the framework has not been well studied, and the benefit of its implementation does not appear to exceed the extra burden on practitioners and teams (133).

Dementia was first included in the process in 2006 (130, 131) and evidence shows an increase in quality of care for people with dementia, including reducing the length of acute care at hospitals when required (136), though I was unable to find evidence that estimates the effect of the framework on dementia diagnosis.

In 2015 and 2016 the UK released its 3-year Directed Enhanced Service 18 (DES18) and the 6-month Dementia Identification Scheme (DIS), respectively, in order to improve the dementia diagnosis rate in primary care among the estimated 67% of community-dwelling cases (137). In addition to financial supports for implementing the QOF, GPs were directly paid an extra amount for every new diagnosis recorded. It is reported that the total number of dementia diagnoses in QOF clinics has impressively improved within a year from the introduction of the DES18 to achieve the proposed target, and the result seems to be continued even after the intervention ended though evidence remains unclear (137). There was also an unexpected improvement in quality of continuity of care for people with dementia, which may be attributed to the extra time GPs spend in making the diagnosis (138). There is now encouragement to expand DES18 and DIS into other diseases (137).

In Canada, the Rising Tide: The Impact of Dementia on Canadian Society report released in 2010 may be considered the first national report on dementia and its related matters (111). The document describes the situation and predicts the

influence of increasing trends in dementia in Canada as a whole. Provincial stages of action on disease prevention and supportive care have also been reported though no Canadian provinces and territories have implemented a separate department to support dementia management, and only Ontario has budgeted funding specifically for dementia care(111). Provincially, up to the time of the Rising Tide publication, British Columbia, Manitoba, Saskatchewan, Ontario, Quebec, and Newfoundland and Labrador had developed specific policies, though they are greatly varied from one province to another (111). Policies for dementia management remain handicapped for a lack of supporting evidence and mostly focus on helping people with the disease and their caregivers. Improvement in diagnosis was only mentioned as an objective in Saskatchewan strategy (111).

In general, most provinces have relatively recently updated their action plan to a strategy. These share similar priorities, such as increasing dementia awareness among community and health care workers, as well as supporting dementia-related research to improve understanding of the disease and its prevention. No studies were identified on the effectiveness of the earlier strategies and frameworks, though it was acknowledged in the newer publications that even though awareness and funding spent on dementia research and care have been increasing over the last two decades in Canada, there is still a lot to do (139). Table 1-2 presents the year that a province published its dementia strategy and/or action plans.

Looking at age-standardized incidence rates by year and province from 2002 to 2015, provided by the Public Health Agency of Canada (figure 1-3), with dots indicates year of provincial strategy publication, there is little evidence for changes in incident dementia associated with publication of a provincial strategy. But, visually, there is an increment in NL starting in 2005 which might be attributable to publication of their action plan in 2004; there also is a steep increment in MB in 2003 and 2004 after the release of their strategy in 2003 and a slight increment in BC since 2007, a year after the province published their strategy. These might

signal increased awareness of the condition in the community with better case finding as a result, but that signal is inconclusive.

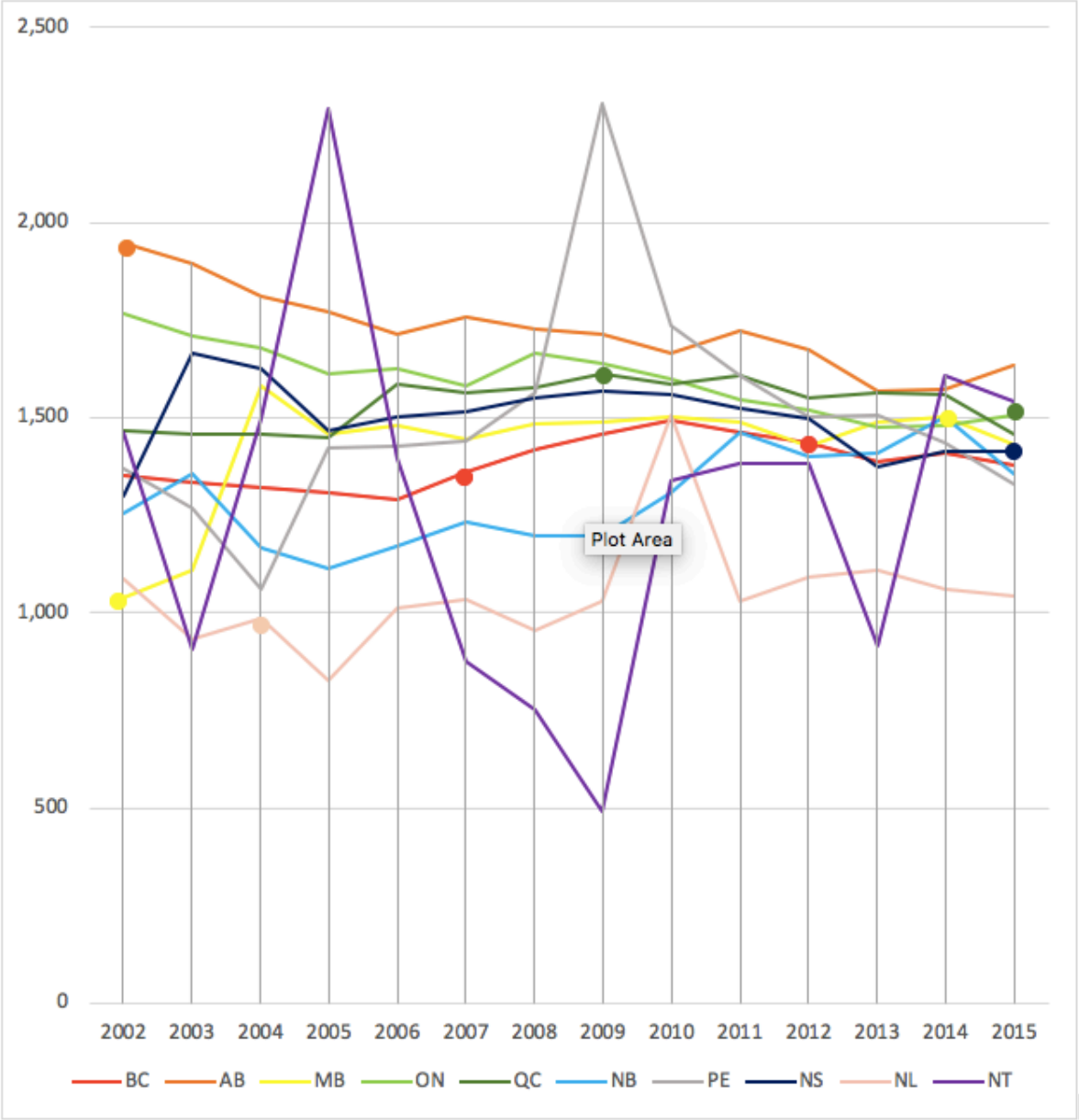
Table 1-2. Canadian provincial strategy for dementia

Province	**First publication**	**Second publication**
British Columbia (BC)	2007 (140)	2012 (141)
Alberta (AB)	2002 (142)	2017 (139)
Saskatchewan (SK)	2004 (143)	Not available
Manitoba (MB)	2002 (144)	2014 (145)
Ontario (ON)	1999 (146)	On-going as of June 2018 (147)
Quebec (QC)	2009 (148)	2015 (149)
New Brunswick (NB)	Not available	2017 (150)
Prince Edward Island (PE)	Not available	Ongoing as of March 2018 (151)
Nova Scotia (NS)	Not available	2015 (152)
Newfoundland and Labrador (NL)	2004 (153)	n/a

The Canadian national dementia strategy, a product of years of working with the involvement of many people from researchers to policy makers and published last July, identifies four priorities Canada should focus on to reduce the future burden of dementia, including research on risk and preventive factors as the first priority (155). It is clear that there has been an increasing concern about dementia over recent years, one clear example being that funding for dementia research has increased substantially, including $200 million over five years from 2014 to 2018 for dementia-related research and $40 million over five years from 2019 to 2024 to increase awareness about dementia prevention and early diagnosis (156).

In conclusion, even though treatments for dementia are still unclear, the most common cardiovascular disease risk factors are considered modifiable, potentially benefiting from treatment or intervention (157). Therefore, studies on cardiovascular disease risk factors may contribute valuable evidence to prevent or delay dementia. Hypertension, diabetes, dyslipidemia and changes in BMI during adulthood are 'targetable' since they are measurable and commonly recorded in health records. To my knowledge, no study has been conducted in Canadian primary care settings to explore whether or not risk factor data included in electronic medical records could predict dementia onset.

Figure 1-3. Dementia, including Alzheimer's disease, age-standardized incidence rate, per 100,000, age 65 years and older by provinces and fiscal year (154)



**** Saskatchewan data was not included for not being available on the Public Health Infobase.***

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CHAPTER 2. EPIDEMIOLOGY OF DEMENTIA ONSET CAPTURED IN CANADIAN PRIMARY CARE ELECTRONIC MEDICAL RECORDS

INTRODUCTION

Dementias are long-term, chronic neurodegenerative conditions which affect cognition and include, but are not limited to, a decline in functional memory, learning ability, and at least one additional domain of cognitive deficit (1). While cognitive decline may often be considered as a normal part of aging, it is a chronic failure caused by progressive physical damage to the brain (2).

As of 2016, there were 47 million people worldwide living with dementia, though the true number may be much higher, since, even in high income countries, including Canada, only 50% of people with dementia are diagnosed (3). In Canada, dementia is the third ranked cause of death (4). In 2008, Canada had over 480,000 people living with dementia (PLWD) and it is estimated that 231 million hours was spent by their family members in caring for them, accounting for $4.9 billion in opportunity costs (5). The Canadian Study of Health and Aging estimated the prevalence of all-age dementia in 2016 at 1.6% and predicted an increase by 66% to about 2.6% in 2031 (6). Economically, Canada committed a total of $10.4 billion a year for dementia care, including $8 billion in direct and $1.8 billion through indirect costs annually; this sum is predicted to double by 2030 (6).

The diagnosis of dementia is complicated; it requires a comprehensive evaluation and evidence of cognitive decline over time, and there is no single diagnostic test for the condition (1, 7). Diagnosis is especially difficult for early-stage dementia, when symptoms and signs are non-specific, rarely recorded by physicians or reported by patients who may rationalize memory loss as being normal for age. Symptoms are more likely to be noticed by a close family member (7). For this

reason, primary care providers in the community are usually the first health professionals to recognize and identify dementia onset and are best placed to provide early support for people with the condition and their families (8).

Since 2006, Canada has not made significant revision to its criteria for a diagnosis of dementia. The Fourth Canadian Consensus Conference on the Diagnosis and Treatment of Dementia in 2012 (9) recommended that clinical diagnosis guidelines remained as in the previous version, published 6 years earlier (10). This paper aimed to identify trends in the incidence of dementia in community-dwelling Canadian seniors over nine years of follow-up.

METHODS

Study population

Participants for this study were Canadians aged 65y and older at any point in time in 2008, whose electronic medical records (EMRs) contributed data to the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) 2017-Q4 (ie December) extraction. The CPCSSN is a pan-Canadian system that records deidentified primary care clinical data, extracted from individual EMRs held by family physicians and other primary care providers (11). Briefly, the CPCSSN database includes patient-level information about diagnoses, prescribed medications, demographics (age, sex, postcode of residence with deprivation index), medical examinations, laboratory test results, referrals, co-morbidities, and risk factors. Started in 2008, CPCSSN has had reliable data that has been used to investigate the incidence, prevalence, and management of various diseases in primary care. CPCSSN extracts de-identified clinical information from EMRs in eight provinces and territories, standardizes their format, and stores them in a high security environment. The data are available for surveillance, research and quality improvement initiatives. The CPCSSN is in its twelfth year of operation, and currently includes data from more than 1.9 million primary care patients.

By the end of 2017, the national CPCSSN database included 36,359 dementia cases, accounting for 2.0% of the whole CPCSSN population. The crude prevalence among people aged 65 years and older was 33,936 cases, accounting for 15.8% of CPCSSN participants aged 65 and older and 93% of all CPCSSN dementia cases.

Selection criteria:

The analysis was applied to a closed cohort of all patients who were born in or prior to 1943 to form a cohort of dementia-free people aged 65 and older on 1st January 2009. Participants must have had at least one encounter with their 'host' family practice clinic before 1st January 2008 and one encounter after 31st December 2013 to ensure being active in the database for at least six years. The year of 2008 was identified as a washout period to reduce undiagnosed dementia cases and ascertain the true incidence of dementia. In other words, all patients with a diagnosis of dementia in 2008 were classified as prevalent cases and were therefore excluded from the analysis.

The first date of active follow-up was 1st January 2009 and the end date of follow-up was the earliest of: (1) the date of dementia diagnosis, (2) two years after the last visit, or (3) 31st December 2017. A flow chart of cohort selection is provided in figure 1.

The CPCSSN case definition for dementia is designed to include all types of the condition. It requires evidence from the health condition (or problem list), encounter diagnosis or billing tables for an ICD-9 code of 290.*, 331.*, 294.1, 294.8, 797.* or 438.*, or a prescription for a cholinesterase inhibitor medication (Rivastigmine, Galantamine or Donepezil) or the N-methyl-d-aspartate (NMDA) antagonist, Memantine (12). Incidence of dementia was defined as an encounter at which a patient's condition first met the validated CPCSSN case criteria for dementia. The CPCSSN dementia case definition has been validated using chart review as the reference standard, with sensitivity of 96.8% (95% CI, 93.3-100.0), specificity of

98.1% (95% CI, 97.5-98.7), positive predictive value of 72.8% (95% CI, 65.0-80.6), and negative predictive value of 99.8% (95% CI, 99.6-100.0) (13).

Statistical analysis

Descriptive analysis comparing demographic and health characteristics between people with and without dementia was conducted using *t*-test for continuous variables (age), and *chi*-square test for categorical variables (sex, rural/urban, and smoking history) (14).

Incident cases were identified for each calendar year; the numerator being the number of cases diagnosed and the denominator the number of people who had at least one visit in that respective year, (i.e. those who still remain in the cohort until the given year). Nine-year cumulative incidence rate and annual incidence rates were calculated as the number of new cases per 1,000 person-years over a respective period of time. Five-year ranges of age and sex-standardized incidence rates (SIRs) were calculated by direct standardized method using data from the Canadian Chronic Disease Surveillance System (15) as the standard. STATA 14 (16) and SQLite (17) were used for the analysis.

Ethics

The CPCSSN database has received ethics approval from each contributing network's local Research Ethics Board, including waivers of individual patient consent for their de-identified data to be used for surveillance and research. This study also was the subject of a formal data sharing agreement with the CPCSSN and received specific approval from the Research Ethics Board at the University of Alberta.

RESULTS

Demographic characteristics of participants

Participants in this study had a mean (standard deviation (SD)) age of 74.1 (6.2) years at entry. About 58% of them were female; 76% lived in urban areas; and 25.7% were identified as smokers.

After nine-years of follow-up, 4,935 (12.6%) patients had been diagnosed with dementia, contributing to a total of 329,733 person-years, mean (SD) period of follow-up was 8.4 (1.5) years. Comparisons of demographic and health characteristics at baseline between patients with and without dementia are presented in table 2-1.

Incidence rates and trends for incidence of dementia

The nine-year cumulative incidence for dementia was 15.0 (95% CI, 14.6-15.4) per 1,000 person-years. Age-standardized annual incidence rates of dementia have increased over time for both males and females, from about 3.4 (95% CI, 2.9-3.8) cases per 1,000 person-year in 2009 to 11.4 (95%CI, 10.5-12.2) in 2014, then slightly drop down to 10.8 (95% CI, 9.9-11.7) cases per 1,000 person-year in 2017. Table 2-2 presents the standardized annual incidence rates of dementia recorded from 2009 to 2017.

Stratifying by birth cohorts of 5-year interval, the incidence in the youngest group (65-69-year-old) was 0.8 (95% CI, 0.5-1.1) cases per 1,000 person-years in the first year increasing to 3.9 (95% CI, 3.2-4.5) cases per 1,000 person-years in 2017. Among people aged 70-74, the incidence was 1.0 (95% CI, 0.7-1.12) cases per 1,000 person-years in 2009 increasing to 4.1 (95% CI, 3.5-4.7) cases per 1,000 person-years in 2017. Among people aged 75-79, the incidence was 1.1 (95% CI, 0.8-1.4) cases per 1,000 person-years in 2009 increasing to 5.1 (95% CI, 4.4-5.8) cases per 1,000 person-years in 2017. Among people aged 80-84, the incidence was 1.6 (95% CI, 1.2-2.0) cases per 1,000 person-years in 2009 increasing to 3.8 (95% CI, 3.1-4.5) cases per 1,000 person-years in 2017. Among the oldest old (people aged 85+) the incidence rate of dementia increases from 2.3 (95% CI, 1.7-2.9) cases per 1,000 person-year in 2009 to 7.5 (95%CI, 6.3-8.8) in 2014, then

declines to 4.8 (95% CI, 3.7-6.0) cases per 1,000 person-years three years later in 2017.

At the same age, people who were born later have higher rates of diagnosed dementia. For example, comparing people aged 70-74 in 2009 and in 2014, the annual incidence rates were 1.0 versus 2.3 cases per 1,000 person-year, respectively. In older groups, the differences are even bigger, for example, the rates in those aged 75-79 in 2008 and in 2014 were 1.1 and 3.3 cases per 1,000 person-year, respectively.

Figure 1-2 shows that the trends for incident dementia are consistently increasing across age group in the whole cohort, except for two decrements around the age of 88 for 80-84-year-old group and 90 for 85-and-over-group.

The incidence rates are slightly higher in females than in males, SIR = 4.1 (95%CI, 3.4-4.8) versus SIR = 2.6 (95%CI, 2.1-3.2) in 2009 and SIR = 11.9 (95%CI, 10.6-13.1) versus SIR = 9.8 (95%CI, 8.6-11.0). Figure 3 and 4 show the same trends of increasing in incidence rates over time for two sexes and urban/rural postal codes.

DISCUSSION

To our knowledge, this is the first study to report the incidence of dementia managed in Canadian primary care using electronic medical record data. The nine-year incidence rate of dementia in this cohort is 15.0 cases per 1,000 person-years, comparable to 14.3 cases per 1,000 person-years reported from Canadian Surveillance Chronic Disease System (CCDSS) (18).

Data recorded in Canadian primary care EMRs show that the incidence of dementia increases with age. This is aligned with previous findings on community-dwelling older adults (19, 20) those claimed that as people are getting older, they are at higher risk of developing dementia.

The overall trend for incidence rates of dementia shows a consistent increase over time associated with age and sex. The incidence of dementia increases steadily and slowly in people aged between 65 and 85 years, adding less than one case per 1,000 person-year for every additional year in the cohort, reaching the peak of 7.5 cases per 1,000 person-years in those aged 90 and older. The rates in females are slightly higher than in males, differences between the sexes are statistically significant. This result was also found in multiple previous studies including those conducted on Swedish, British, and US general populations (20-23).

Existing evidence from multiple cohort studies suggests that in the same age range, those who were born later have lower rates of developing dementia as the attribution of multiple factors including higher education and better healthcare to control cardiovascular diseases and conditions (24, 25). In opposition to this, our study found higher rates for people who were born in later years. It may be true that the actual incidence of dementia is starting to reduce in a few recent years (15, 26) and people who were born in more recent years are less likely vulnerable to dementia than previous generations for having access to better education and healthcare; however, the number of cases being identified is still growing over time. In other words, risk at individual level may be declined in a few recent years but at population level, the risk of being diagnosed with dementia continues to increase. The same trend has been observed in the UK with prevalence of dementia diagnosis in primary care data increased two times over a 10-year period. This finding might be contributed to the publication of the UK National Dementia Strategy (27). It is unclear if there is a specific modification in primary care practice in Canada that leads to the impressive increase in the number of new dementia diagnosis. However, it is believed this may be caused by changes and improvement in the quality of data input by family practitioners, the improvement of completeness in EMR, and a result of the greater attention paid to diagnosing and managing dementia in primary care in the last few years.

We observed a slowing rate of new cases from 7.5 cases per 1,000 person-years in 2014, down to 6.0 cases per 1,000 person-years in 2015 and 4.8 cases per 1,000 person-year in 2017 when the oldest sub-cohort reached the age of 95+. The reduction in the 80-84 year-old group of females occurred earlier than in the oldest males (2015 for females versus 2016 for males); among the oldest old, both sexes experienced a decrement in the same year of 2015. Meta-analysis using previously conducted cohorts are contradictory; one supports our findings and reported dementia incidence rates is 2 per 1,000 person-years for the 65-75 age group, falling to 1.5 per 1,000 person-years for people aged 85 (28); the other found that the incidence and prevalence of dementia increased after the age of 85, more rapidly in females than for males (29).

Our study supports the hypothesis of competing risk of mortality (30). This suggests that people with better mid-life living conditions, having higher educational attainment, greater access to health care with better mental, physical and social behaviours and health as well as being less exposed to a variety of chronic disorders and risk factors, tend to live longer and are more likely to be protected from dementia. Because death date records are not included in CPCSSN data, we were unable to include competing risk of death for 1,742 (4.5%) dementia-free persons who left the cohort before the end date in this analysis. The trend of slowing incidence rates among the oldest old has also been noted in studies of other chronic diseases, such as stroke or cardiovascular disease, which might indirectly reduce dementia onset. It is also possible; however, this population are more likely to be underdiagnosed than younger old persons (31). Regardless, factors that contribute to the lower incidence rate of dementia among the very old persons have not been clearly identified.

Our data show the same trends of increasing incidence rates in both rural and urban groups of people, though the standardized incidence rates in urban areas are significantly higher than in rural areas in the first two-third of the follow-up period. For example, 7.1 versus 5.4 in 2009 and 24.0 versus 18.4 cases per 1,000

person-years in 2014. Since 2015, the differences between two groups become smaller. These findings may be influenced by limited access to primary care and community support services in rural neighborhoods. Awareness of dementia among patients and their family members in rural and remote communities may be less well developed which may lead to a lower rate of diagnosis in these areas (32, 33). In addition, a lower number of physicians per capita is also a barrier which may contribute to increase the number of undiagnosed dementias in rural communities (34).

Strength and limitations

The main advantages of the secondary use of routinely collected, population-based, clinical data for research are its low cost and availability, combined with significant benefits of a cohort design in which a large sample with arguably complete information will increase the precision of outcome estimates. Having a large and ready-to-use sample like that from CPCSSN reduces financial, human, and other costs, especially when considering dementia, a fairly long latency chronic condition. Furthermore, as about half of an average family physician's patients are estimated as being people living with chronic disease, data from primary care settings are ideal for studying disease with a long latency period such as dementia. Also, data are collected prospectively and systematically by practitioners, which should minimize information bias (35). Including only those with at least six years of records since the first day of follow-up reduces missing cases and inaccurate results.

This study also has some limitations. We were not able to fully assess competing risks attributable to factors either not known or not recorded in the clinical record, such as death, or moving to a long-term care institution. These are significant limitations. Though the clinical use of primary care EMR data becomes more common, more complete and comprehensive data should accrue in the future. Dementia cases not diagnosed by primary care providers may not be recorded in the EMR. Also, this study has used a very high validity case definition from

CPCSSN to minimize the chance of misclassification and self-selection bias; however, these may still be expected given the imperfect nature of almost all case definition algorithms (36).

In conclusion, the incidence of dementia has increased in the last few years and are expected to continue to do so unless effective preventive strategies are employed. Future studies should identify potential risk and protective factors for dementia in order to provide evidence for new policies in developing a national preventive strategy for dementia. The next paper in this thesis will examine risk factors for incidence of dementia to further investigate findings from this paper. Also, in the future, CPCSSN will clearly have more data on the oldest old group of people, as well as more data on risk factors for chronic diseases. Future studies should also consider the oldest old separately in a sub-analysis to avoid survival bias.

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Figure 2-1. Flowchart of cohort identification

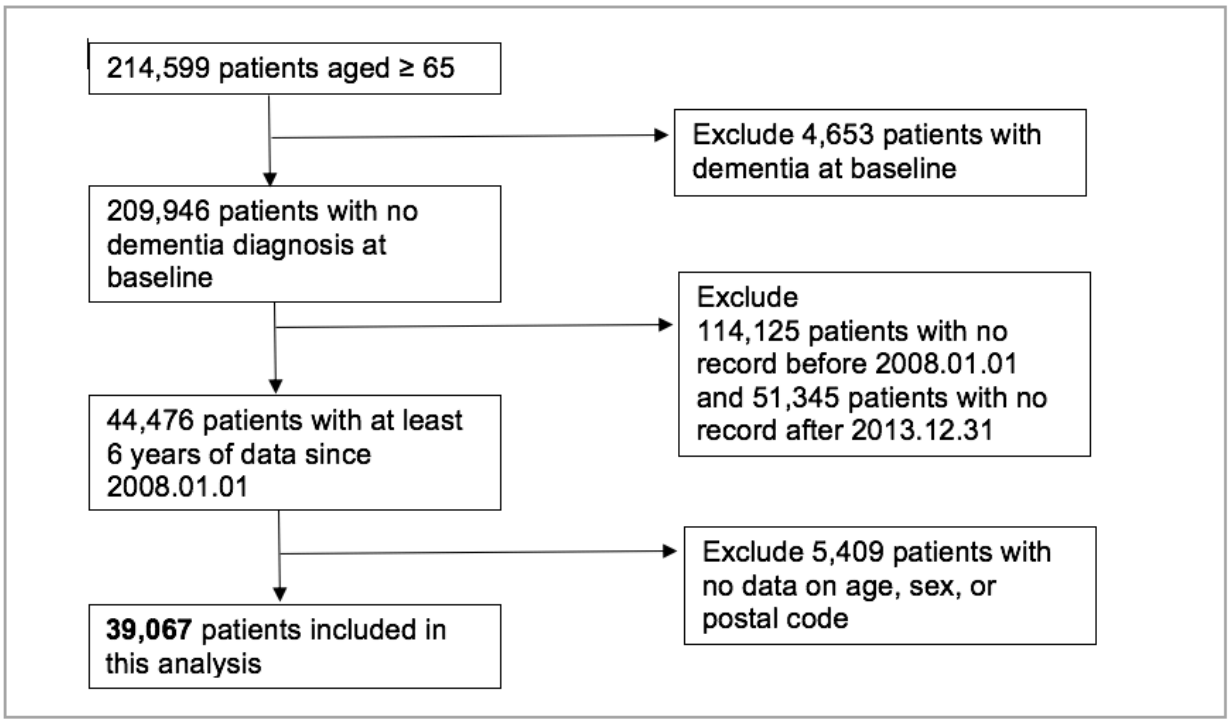


Table 2-1. Demographic and health characteristics of people who developed and did not develop incident dementia during follow-up

	Dementia-free people	People with dementia	p-value for difference*
n	34,132	4,935	N/A
Mean age ± SD	*73.5 ± 6.0*	*77.7 ± 6.4*	*< 0.001*
Females %	*19,528 (57.2)*	*2,957 (59.9)*	*< 0.001*
Urban %	*25,799 (75.6)*	*3,900 (79.0)*	*< 0.001*
Smokers %	25,342 (74.3)	3,681 (74.6)	0.565
Deprivation index*			*< 0.001*
1st quintile (least deprived)	5,109 (15.24)	642 (13.29)	
2	7,531 (22.46)	1,119 (23.17)	
3	8,220 (24.52)	1,127 (23.34)	
4	5,959 (17.77)	946 (19.59)	
5th quintile (most deprived)	6,709 (20.01)	995 (20.6)	

Crude numbers are presented in the above table.

* deprivation index includes social and material deprivation indices, calculated from Canadian Census data using postal code (http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?printer=Y&conceptID=1415)

Table 2-2. Age-standardized annual incidence rates of dementia

Year	Persons at risk	Crude incidence rate (%)	Standardized incidence rate (%) [95% CI]
2009	39,067	6.1	3.4 [2.9-3.8]
2010	38,829	8.7	5.0 [4.4-5.5]
2011	38,491	9.7	5.3 [4.7-5.9]
2012	38,117	13.6	7.5 [6.9-8.2]
2013	37,599	15.7	8.7 [8.0-9.5]
2014	37,008	20.2	11.4 [10.5-12.2]
2015	36,260	20.5	11.1 [10.2-11.9]
2016	35,517	20.0	10.5 [9.6-11.3]
2017	33,064	20.4	10.8 [9.9-11.7]

Figure 2-2. Annual incidence rates for both sexes by age at baseline

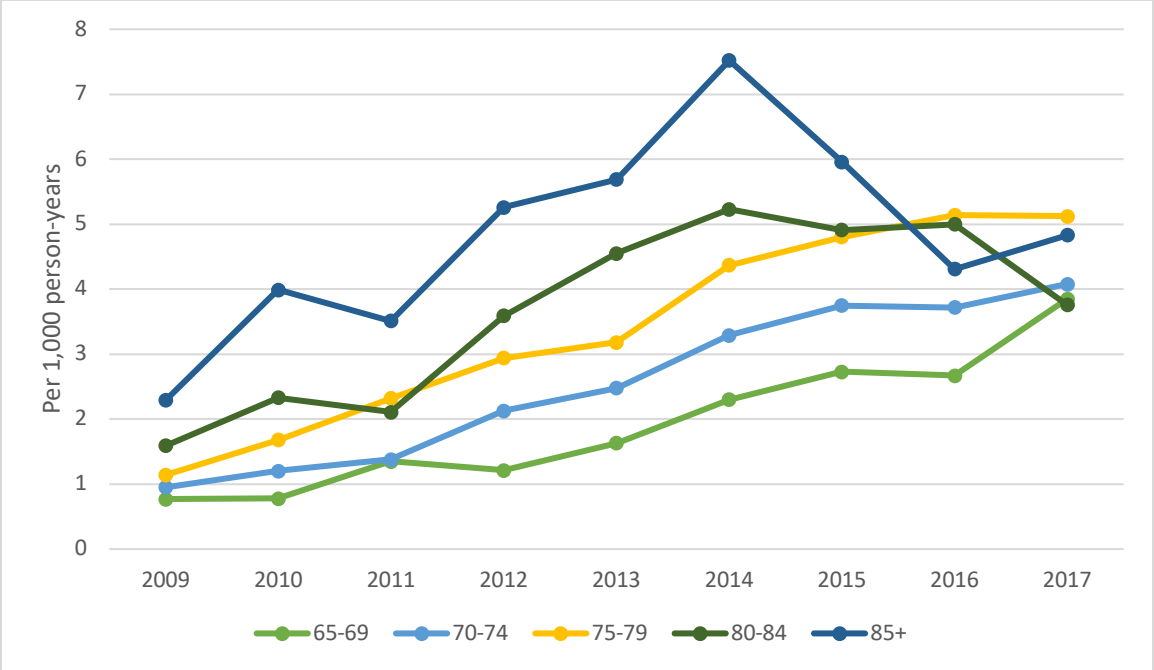


Figure 2-3. Age- and sex-standardized annual incidence rates of dementia by sex

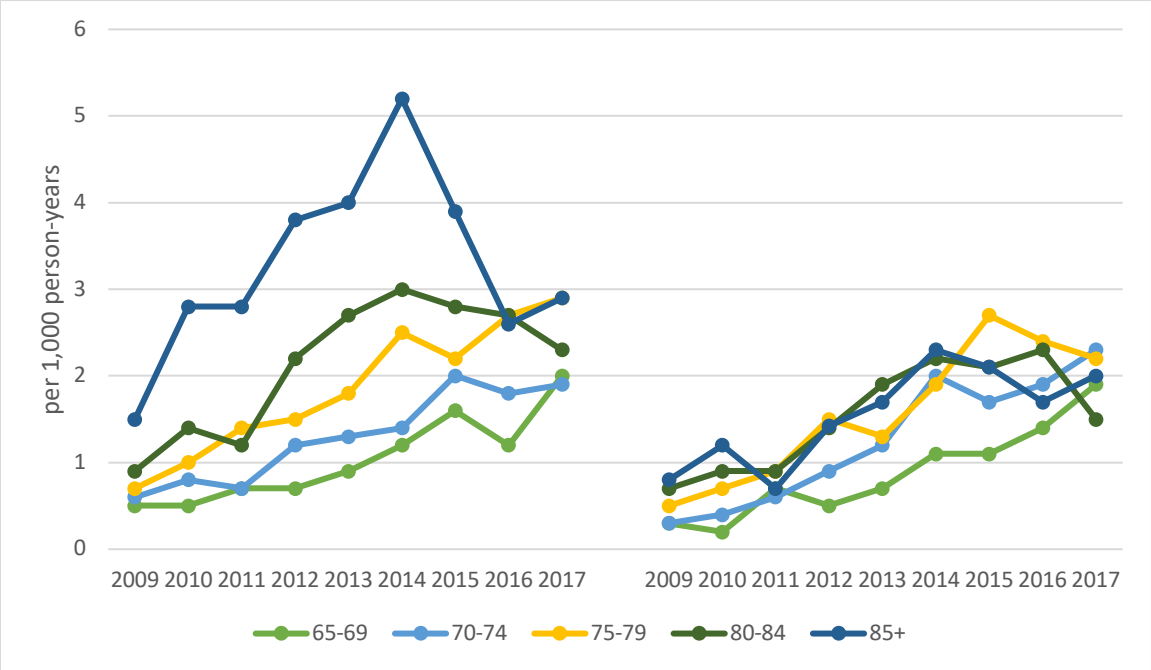
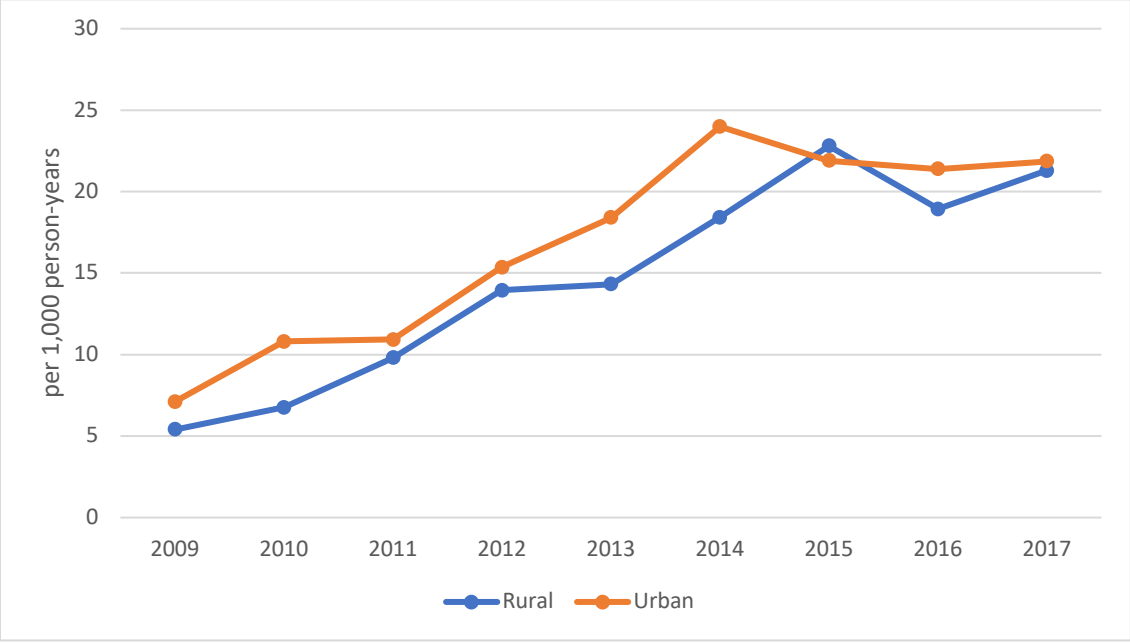


Figure 2-4. Age and sex-standardized incidence rates by urban/rural status



CHAPTER 3. RISK FACTORS FOR INCIDENCE OF DEMENTIA IN PRIMARY CARE PRACTICE: A RETROSPECTIVE COHORT STUDY IN OLDER ADULTS

INTRODUCTION

In the last thirty years, dementia has gained the attention of researchers resulting in an increase in the quality and quantity of studies assessing the impact of associated risk factors and identifying areas of preventability (1). However, even though individual longitudinal studies show that modifiable cardiovascular risk factors (e.g. physical inactivity, smoking, hypertension, obesity, and diabetes), depression, and low educational attainment may be associated with Alzheimer's disease (2, 3), the relationship between late life risk factors and subsequent dementia onset remains unconfirmed. Meta-analyses and systematic reviews have concluded that the evidence is not sufficiently consistent to indicate a clear causal association between dementia onset and hypertension (4). Though an association with vascular dementia is clearer (5) while dyslipidemia has been reported both as a protective factor and a risk factor for dementia (6).

The aim of this study was to analyze routinely collected primary care electronic medical record (EMR) data to quantify the potential effect of modifiable risk factors, comorbidity, and demographic characteristics (age, sex, rurality, deprivation category) on the incidence of dementia in community-dwelling Canadians aged 65 and older.

METHODS

Study design

This was a retrospective cohort design. Data were extracted from primary care electronic medical record data held by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) (7). Participants included people who were active

in the CPCSSN dataset as of the December 2017 extraction, were aged 65y or older at any time in 2009, whose records included required demographic data (sex, age, postal code and deprivation index) and a minimum of six years of recorded data from January 01, 2008 to December 31, 2013. All patients with a diagnosis of dementia in or before 2008 were excluded from the analysis as being prevalent cases. The index date for the study was January 01, 2009 and the end date was when the earliest of any one of the following conditions existed: the date of dementia diagnosis, two years after the last recorded visit, or December 31, 2017. A flowchart of the development cohort is provided in figure 1.

Data source

Started in 2005, CPCSSN is the only national Canadian data platform for EMR-based primary care research and is ideally positioned to close the gap between research, clinical practice and health policy (8). The system records clinical information, including patient-level information about diagnoses, prescribed medications, demographics (age, sex, postcode of residence and deprivation index), medical examinations, laboratory test results, referrals, co-morbidity and risk factors (9). Data are derived every 6 months from primary care EMRs produced by a variety of vendors, deidentified (9), cleaned and organized into a standard format (10, 11). This uses the same names and codes for each specific variable, based on the Anatomical Therapeutic Chemical (ATC) Classification System for medications and the International Classification of Diseases, Ninth Revision (ICD-9) for disease diagnosis (12). As of 2017, CPCSSN included 373,373 patients older than 64 years representing 20.4% of its total population; people aged 65y and older accounted for 14.8% in the Canadian general population 2011 census. These numbers may reflect the fact that older adults have more health concerns than younger adults and hence are more likely to contact their family physicians. The ratio of sex in the CPCSSN was 0.79 males to females, approximating to the census ratio of 0.80 (13).

Case definitions

The CPCSSN case definition for dementia is a comprehensive algorithm designed to include all types of the condition. It requires evidence from either free-text fields or drop-down menus of the health condition (or problem list), encounter diagnosis or billing tables for an ICD-9 code of 290.*, 331.*, 294.1, 294.8, 797.* or 438.*, or a prescription for a cholinesterase inhibitor (Rivastigmine, Galantamine or Donepezil) or an N-methyl-D-aspartate (NMDA) receptor antagonist (Memantine) (14). Incidence of dementia date is defined as a clinical encounter recorded in the EMR at which a patient first met the validated CPCSSN case criteria for the condition.

Patients with hypertension, diabetes mellitus, and depression are also identified with evidence from patients' problem list, encounter diagnosis, billing, medication tables, and/or lab test results (14). All CPCSSN case definitions have been validated using either EMR chart or CPCSSN record review as a gold standard, with sensitivity 96.8% (95% CI, 93.3-100.0), specificity 98.1% (95% CI, 97.5-98.7), positive predicted value 72.8% (95% CI, 65.0-80.6) and negative predicted value 99.8% (95% CI, 99.6-100.0) (15).

Dyslipidemia cases are defined in this analysis as having a combination of one prescription of lipid-lowering medications (ATC code C10) and one abnormal blood lipid reading for any type of cholesterol, or one occasion of being diagnosed with dyslipidemia (ICD-9 code 272.4). This definition has been validated using CPCSSN data yielding a sensitivity of 98%, specificity of 100%, positive predictive values of 100% and negative predictive values of 93% (16).

Being underweight is defined by median prior to baseline (January 01, 2009) body mass index (BMI) less than 20.0; and being obese is defined by median prior to baseline BMI greater than or equal to 30.0 or physician diagnosis of obesity (ICD-9 code 278.00, 278.01, 278.03). Patients who were not identified as either underweight or obesity including those without a BMI measurement were assumed

not to have these conditions (normal weight). Any record of BMI less than 10.0 or greater than 70.0 is assumed to be incorrectly input.

Participants were considered to be smokers if they had at least one indicator of smoking in their EMR, including being current or past smokers before baseline; non-smokers were those who had never smoked before baseline. People with no record of smoking were assumed to be never smokers.

Medications use was defined as having received at least one prescription within the two years before baseline. ATC codes were used to identify medications. Antihypertensive medications include codes antihypertensive (C02*); diuretics (C03*) with the exception of diuretics used primarily for heart failure, or other oedematous states – furosemide (C03CA01), bumetanide (C03CA02) and metolazone (C03BA08); peripheral vasodilators (C04*); beta blocking agents (C07*), Calcium channel blockers (C08*); and agents acting on renin-angiotensin system (C09*). Statin drugs included atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin (ATC codes C10AA* and C10B*).

Statistical analysis

Incidence of dementia was compared among those exposed and those unexposed to the selected risk factors in order to identify demographic and health characteristics of people who did and did not develop incident dementia during follow-up. Survival analysis with Cox's proportional hazard was performed to estimate hazard ratios (HR). All steps of the analysis from data management to inferential analysis have been done in SQLite (17) and STATA 14 (18).

Ethics

The CPCSSN database has received ethics approval from each contributing network's local Research Ethics Board, including waivers of individual patient consent for their de-identified data to be used for surveillance and research. This

study received specific approval from the Research Ethics Board at the University of Alberta and the investigator signed a data sharing agreement with the CPCSSN.

FINDINGS

Over a follow-up period of nine years, 39,066 eligible participants contributed to a total of 329,731 person-years at risk, with 4,935 new cases of dementia identified. As previous evidence found a sharp increase in dementia incidence after the age of 80y (19), this analysis was conducted for two age groups, patients aged 65-79y and those aged 80y and over at baseline. There were 31,185 participants aged 65-79 years and 7,881 aged 80 years and over. The older group included more females (63.8% versus 56.0%, $p < 0.001$) and those who resided in an urban postal code (79.1% versus 75.3%, $p < 0.001$) than the group of people aged 65-79y. The percentage of people recorded as having ever smoked was 21.4% of those 80y and older and 26.8% ($p < 0.001$) of the 65-79-year-olds. Except for hypertension and osteoarthritis, which had higher prevalences in the older group, a lower prevalence was found among them for other chronic conditions, including diabetes mellitus, dyslipidemia, obesity, and depression in comparison to the younger one. Table 3-1 presents baseline characteristics of the two age groups, and also of the entire cohort under study.

Patients aged 65-79y included 267,996 person-years at risk with 3,012 dementia cases. after adjusting for comorbidities and demographic characteristics, the rate of dementia onset increased by 13% for every additional year in age, HR = 1.13 (95%CI, 1.12-1.14) among people age 65-79. People living in more socially deprived postcodes (deprivation quintile 3, 4 and 5) also had a higher risk of a dementia diagnosis than people in the least deprived quintiles ($p = 0.001$), although there was no statistically significant relationship between quintile 1 and 2. Depression, osteoarthritis and diabetes mellitus significantly increased the risk of incident dementia (p-value < 0.01). Sex, material deprivation (identified by 3-digit

postalcode), hypertension, obesity, underweight, and dyslipidemia did not have a statistically significant association with dementia onset.

In the older group, 7,881 patients contributed 61,737 person-years at risk; only three variables significantly predicted dementia onset. Age increases risk at a lower rate of 5% for every one additional year in age, HR = 1.05 (95%CI, 1.03-1.06). Patients with a diagnosis of depression are also at higher risk, HR = 1.33 (95%CI, 1.11-1.60), older adults with underweight at higher risk than normal weights, HR = 1.84 (95% CI, 1.26-2.67). Table 3-2 presented adjusted hazard ratios of dementia onset for the two groups.

Two *post hoc* analyses, replacing hypertension and dyslipidemia with antihypertensive and statin use, one at a time, were performed. After controlling for demographic characteristics and other chronic diseases, no significant association was found for either age groups (table 3-3).

DISCUSSION

Overall, after a follow-up of 8.4 ± 1.4 years, in 39,066 Canadian primary care patients aged 65y and over, this study found that incidence of dementia was associated with age but not with sex and rurality in all ages. There was a positive association with history of smoking, social index, depression, osteoarthritis and diabetes mellitus among people aged of 65-79y at baseline. However, among those aged 80y and over at baseline, only associations with material index and depression were statistically significant. In comparison to Statistics Canada reports (20, 21), the prevalence of chronic conditions in this cohort, including smoking, hypertension, diabetes, dyslipidemia and obesity is slightly lower in those living in urban settings. A possible reason is that the case definitions used for these conditions in this study were more stringent and thus more conservative. Using multiple criteria such as clinical diagnosis or prescription of relevant medications may lead to a more valid estimate than those employed by Statistics Canada which

mainly used self-reported data (21). Also, a gap of 8 years in the two sets of statistics (2008 for the study cohort and 2016 for the Statistics Canada sample) may be significant since the proportion of Canadian people aged 65y and older increased from 13.9% in 2009 to 16.9% in 2017 (22, 23). This might be associated with an increased prevalence of other chronic diseases in the community.

Hypertension

Evidence regarding the effect that hypertension has on dementia incidence is conflicting. Some studies suggest a positive association (24-29) while others find negative effects (30-33). In the current study there was a non-significant association between hypertension and subsequent dementia diagnosis for participants in all ages. This concurs with a number of other longitudinal studies on both vascular dementia and Alzheimer's disease (34). A potential explanation for this is that most hypertensive people recorded in primary care data are treated and have reasonably well-controlled blood pressure which reduces damage and complications to a point that hypertension ceases to be a risk factor. The same scenario has been claimed for stroke (35).

However, among uncontrolled hypertensive patients, previous studies have found that more severe high blood pressure was not a statistically significant predictor (28, 36). While the relationship between hypertensive medication and dementia is also unclear, meta-analyses have found inconsistent evidence for the association between blood pressure drug treatment and dementia incidence (37); however, recent findings from a British study using routinely collected health data found a positive association (38). The *post hoc* analysis performed here replacing hypertension status with either use or not use of antihypertensive medication during the last two years before baseline, found no significant association with subsequent dementia incidence.

Diabetes mellitus

Evidence for an increased risk of incident dementia in patients with diabetes is relatively consistent in most published studies (39-46). Here, people in the younger

group with a diabetes diagnosis before baseline were 1.19 times at higher risk than those without diabetes ($p < 0.001$), compared to 1.33 times from a study in the UK (38). The UK study and this one both used health data from primary care and found that the risk of dementia was reduced with age by 14% and 13% among patients aged 80 to 95 years, respectively (38), though the current study finds this association was not statistically significant.

Dyslipidemia

Patients with dyslipidemia experienced a non-significant 4% greater risk of incident dementia in people aged 65 -79y and an also non-significant 4% lower risk in people aged 80 and older. This is consistent with other studies (47, 48). However, some studies report a lower risk of dementia in people older than 85y associated with higher cholesterol level (47, 49), while others show increment in risk (49-51). As dyslipidemia case definitions are not consistent between studies, different classification may lead to different findings. This study applied a relatively broad (and validated) case definition, but blood cholesterol levels are relatively easily changed according to dietary variation and this may have overestimated the prevalence of dyslipidemia.

The use of statins was not significantly associated with dementia onset, replicating the finding from the UK (38). This is unsurprising as 98% of people with dyslipidemia in this cohort were treated with a statin.

Obesity and underweight

Median baseline BMI ≥ 30 and/or having a diagnosis of being obese of any type recorded in the medical records was negatively, though insignificantly, associated with dementia onset. It is associated with a reduction in risk of 7% and 8% respectively, in the younger and older age groups. This is in contrast to evidence that obese patients (BMI greater than 29.9) have a greater risk of dementia than those who have a ‘normal’ BMI (52-54).

However, we found that BMI lower than 20.0 in people older than 79 years old highly significantly increased the risk of subsequent dementia by 84%; this association is not statistical significance in the younger group. It aligns with a few previous studies which found that (1) lower BMI increased the risk of dementia (55, 56), and (2) people who were underweight had a relatively higher risk of subsequent dementia than those of normal weight (57). This could become apparent years before diagnosis since dementia has a relatively long latency which occurs without perceptible symptoms (58). Under-diagnosis of dementia is common due to limited resources in primary care, physicians are often reluctant to commit to a diagnosis prematurely (59), and/or patients and their families may also be hesitant to identify a problem (60), which may lead to an argument that dementia has already occurred (though not being diagnosed) among the oldest old whose weight is significantly lost. Therefore, an analysis using categories of BMI as predictors may clarify the association between weight in late life and dementia onset. It is of interests to understand if losing weight in old age might be an early sign of latent dementia or vice versa.

Other comorbidities

Even though the pathological mechanism of the association between depression and subsequent dementia is still unclear, the association itself is known (61, 62) and replicated in this study. As for osteoarthritis, a recent meta-analysis which included participants from a variety of age ranges found that its occurrence increases the risk of dementia (63). Our study found the same result for people aged 65 to 79 but not for the very old group.

Strength and limitations

To our knowledge, this is the first study to explore the occurrence and associated outcomes of risk factors prior to a diagnosis of dementia in pan-Canadian primary care. Previous studies have faced difficulties in finding a representative population because the very people at risk for dementia are often excluded from studies or their data are unavailable. In conducting a retrospective longitudinal follow-up

study using available and accessible information in CPCSSN-processed EMR data, the challenge of a non-representative sample of the Canadian population is minimized. Moreover, implementing a dementia-free cohort allows us to have a highly precise denominator for incidence rate calculation and survival analysis.

However, the current database limits the opportunity of accurately evaluating competing risks from other possible factors in dementia incidence, such as inherited genetic conditions, physical inactivity, or mental illnesses other than depression. Though primary care data might be the ideal source from which to study chronic disease, many listed factors are not validated in current Canadian EMR data.

As this cohort includes patients who have at least five years of follow-up data, bias due to loss to follow-up is minimized. Even though information bias due to misclassification is possible as case definitions rarely achieve validation metrics of 100%, it is also minimized by the high validity of CPCSSN case definitions. Other information biases, such as recall bias or interviewer bias, are expected to occur at very low frequency as information was routinely entered by clinicians at the time of providing health care.

CONCLUSION

Diabetes mellitus, depression, osteoarthritis, and underweight but not hypertension, obesity or dyslipidemia managed in primary care is associated with an increased risk for incident dementia diagnosis. Used with caution, routinely collected clinical data are a good for studies with models which include more related variables to provide a more complete picture of dementia's risk and protective factors. Further work is necessary to better understand the apparent association between weight and incidence of dementia.

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Figure 3-1. Flowchart of cohort identification

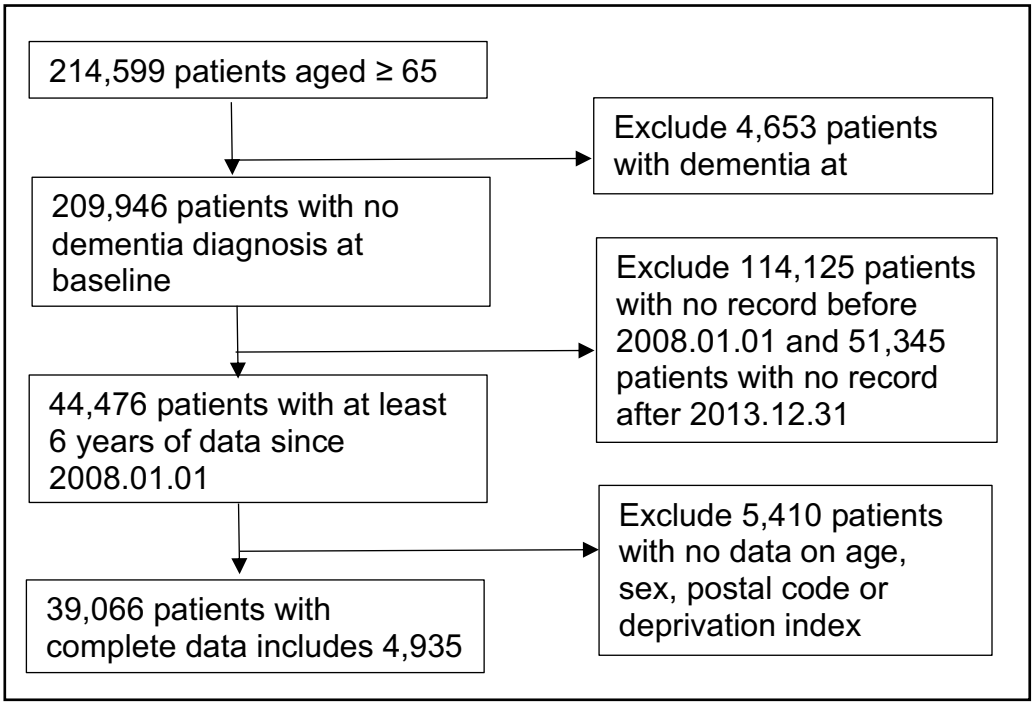

Table 3-1. Demographic and health characteristics at baseline of participants by age group

	All participants	**65-79 years old**	**80+ years old**	**p-value**
n	39,066	31,185	7,881	N/A
person-years at risk	329,731	267,996	61,737	N/A
Age at baseline (mean ± SD)	74.1 ± 6.2	71.6 ± 4.0	83.8 ± 3.4	N/A
Female n, (%)	22,484 (57.6)	17,454 (56.0)	5,031 (63.8)	< 0.001
Urban n, (%)	29,699 (76.0)	23,467 (75.3)	6,232 (79.1)	< 0.001
Smokers n, (%)	10,042 (25.7)	8,355 (26.8)	1,687 (21.4)	< 0.001
Social index				< 0.001
1 (least deprived)	5,853 (15.0)	4,795 (15.4)	1,058 (13.4)	
2	9,215 (23.6)	7,540 (24.2)	1,675 (21.3)	
3	8,230 (21.1)	6,660 (21.4)	1,570 (19.9)	
4	6,919 (17.7)	5,503 (17.7)	1,416 (18.0)	
5 (most deprived)	8,849 (22.7)	6,687 (21.4)	2,162 (27.4)	
Material index				< 0.001
1 (least deprived)	8,314 (21.3)	6,504 (20.9)	1,810 (23.0)	
2	6,502 (16.6)	5,302 (17.0)	1,200 (15.2)	
3	6,778 (17.4)	5,485 (17.6)	1,293 (16.4)	
4	9,188 (23.5)	7,364 (23.6)	1,824 (23.1)	
5 (most deprived)	8,284 (21.2)	6,530 (20.9)	1,754 (22.3)	
Comorbidities				
Depression n, (%)	2,274 (5.8)	1,848 (5.9)	426 (5.4)	0.078
Osteoarthritis n, (%)	6,220 (15.9)	4,707 (15.1)	1,513 (19.2)	< 0.001
Hypertension n, (%)	13,900 (35.6)	10,638 (34.1)	3,262 (41.4)	< 0.001
Diabetes mellitus n, (%)	5,644 (14.5)	4,586 (14.7)	1,058 (13.4)	0.004
Dyslipidemia n, (%)	15,013 (38.4)	12,277 (39.4)	2,736 (34.7)	< 0.001
Underweight n, (%)	249 (0.6)	178 (0.6)	71 (0.9)	< 0.001
Obesity n, (%)	3,858 (9.9)	3,326 (10.7)	516 (6.6)	< 0.001

Table 3-2. Hazard ratios of dementia onset by age groups at baseline

	65-79 years old		**80+ years old**	
Characteristics	AHR [95% CI]	p-value	AHR [95% CI]	p-value
Age	1.13 [1.12-1.14]	< 0.001	1.05 [1.03-1.06]	< 0.001
Sex				
Male	1.01 [0.94-1.09]	0.747	0.95 [0.86-1.04]	0.254
Living area				
Urban	1.05 [0.95-1.16]	0.359	1.08 [0.95-1.24]	0.239
Smoking history				
Smokers	1.09 [1.01-1.18]	0.037	1.01 [0.91-1.13]	0.807
Social index				
1 (least deprived)	1.00		1.00	--
2	1.12 [0.98-1.27]	0.101	0.86 [0.73-1.02]	0.086
3	1.27 [1.12-1.45]	< 0.001	1.15 [0.98-1.36]	0.082
4	1.35 [1.18-1.54]	< 0.001	1.12 [0.95-1.33]	0.180
5 (most deprived)	1.41 [1.24-1.60]	< 0.001	0.95 [0.81-1.12]	0.573
Material index				
1 (least deprived)	1.00		1.00	--
2	1.00 [0.89-1.13]	0.958	0.80 [0.69-0.92]	0.003
3	0.98 [0.87-1.10]	0.699	0.82 [0.71-0.94]	0.006
4	1.08 [0.97-1.21]	0.173	0.94 [0.82-1.08]	0.407
5 (most deprived)	0.98 [0.87-1.10]	0.763	0.75 [0.65-0.87]	< 0.001
Comorbidities				
Depression	1.38 [1.20-1.58]	< 0.001	1.33 [1.11-1.60]	0.002
Osteoarthritis	1.15 [1.05-1.26]	0.004	1.10 [0.98-1.23]	0.108
Hypertension	0.96 [0.89-1.04]	0.305	0.94 [0.86-1.03]	0.207
Diabetes	1.19 [1.08-1.32]	< 0.001	1.14 [1.00-1.30]	0.053
Obesity	0.93 [0.82-1.05]	0.254	0.92 [0.76-1.12]	0.381
Underweight	1.11 [0.72-1.70]	0.642	1.84 [1.26-1.67]	0.001
Dyslipidemia	1.04 [0.96-1.12]	0.329	0.96 [0.87-1.06]	0.403

Table 3-3. Post hoc analysis to access the association between related medication and the risk of dementia onset

	65-79 years old		**80+ years old**	
Characteristics	AHR [95% CI]	p-value	AHR [95% CI]	p-value
Antihypertensive				
No	1.00		1.00	
Yes	1.02 [0.94-1.10]	0.714	0.91 [0.82-1.00]	0.052
Statin				
No	1.00		1.00	
Yes	1.07 [0.98-1.17]	0.110	0.93 [0.83-1.04]	0.219

CHAPTER 4. MULTI-DIMENSIONAL ANALYSIS TO APPROACH THE ASSOCIATION BETWEEN BODY MASS INDEX RECORDED IN PRIMARY CARE PRACTICE AND INCIDENCE OF DEMENTIA

INTRODUCTION

Regardless of obesity being a common risk to healthy aging, its effect on dementia risk remains unclear. An inverted U-shaped association is often seen, with obesity in mid-life increasing the risk of a subsequent dementia diagnosis while late life obesity appears to be protective (1). Other research has reported the absence of statistically and clinically significant associations between obesity and dementia (2). Interestingly, a number of recent studies have reported a protective effect of being overweight or obese in later life (3, 4). This may be true, but the association might be confounded if people who subsequently acquire dementia lose weight rapidly in the period before diagnosis compared to people of the same age who have not yet been diagnosed with dementia (5). This study examines the association between BMI in late life and dementia onset; thus, differences in BMI between people before and after and with and without a dementia diagnosis in primary care are compared to take this into account.

METHODS

Study design and selection criteria

A retrospective cohort design with embedded case-control study was conducted in a sample of dementia-free patients aged 65 years and older in 2009. Participants were required to have at least one visit to their primary care clinic before January 01, 2008 and one after December 31, 2013 to ensure at least six continuous years of follow-up. The first date of active follow-up for the study (the baseline) was January 01, 2009 and the end date of follow-up was the earliest of either (1) date of dementia diagnosis, (2) two years after their last visit, or (2) December 31, 2017.

To be eligible for the study participants required complete demographic data (sex, age, postal code and deprivation index) and at least two measurements of BMI within five years before baseline. Patients with a diagnosis of dementia in or before 2008 were excluded for being prevalence cases.

The study was conducted in two stages. The first was performed on the whole eligible cohort to predict the risk of dementia onset. The second was a nested case-control study where cases were defined as eligible participants with a dementia diagnosis during the follow-up period and who had at least two BMI values before and two values after the date of dementia diagnosis (index date). This is to maximize accuracy of the effects of BMI at the baseline on dementia onset. Four controls were automatically randomly selected for each case from the pool of subjects that did not have dementia. At baseline, cases and controls were matched on 5-year-range age, sex and number of comorbidities using with the validated Canadian Primary Care Surveillance Sentinel Network (CPCSSN) case definition (6). The index date of a case was assigned to be the index date of its matched controls. Figure 1 presents a flowchart of inclusion and exclusion criteria of participants.

Setting

Data for this study were extracted from the December 2017 CPCSSN database. This is a pan-Canadian platform for Electronic Medical Record (EMR)-based primary care research into chronic diseases, which includes clinical information on almost two million people across Canada (7). CPCSSN data include patient-level information about diagnosis, prescribed medications, demographics (age, sex, postcode of residence, and deprivation index), medical examinations, laboratory test values, referrals, co-morbidities, and risk factors (8). All information is de-identified, cleaned, organized into a standard format, and securely held at the Centre for Advanced Computing at Queen's University (9, 10). Data are standardized, based on the Anatomical Therapeutic Chemical (ATC) Classification System for medications and International Classification of Diseases, Ninth

Revision (ICD-9) for disease diagnosis (11). As of 2017, CPCSSN included data from 373,373 patients older than 64 years old, representing 20.4% of the total sample.

Dementia case definitions

Dementia cases were identified through indicators from the EMR health condition (or problem list), encounter diagnosis or billing tables for an ICD-9 code of 290.*, 331.*, 294.1, 294.8, 797.* or 438.*, or a prescription for cholinesterase inhibitor medication (Rivastigmine, Galantamine or Donepezil) or the N-methyl-d-aspartate (NMDA) medication (Memantine) (6). The CPCSSN case definition metrics for dementia provide sensitivity of 96.8% (95% CI, 93.3-100.0), specificity of 98.1% (95% CI, 97.5-98.7), positive predictive value of 72.8% (95% CI, 65.0-80.6), and negative predictive value of 99.8% (95% CI, 99.6-100.0) (12).

BMI measurement and data collection

Weight and height of patients are frequently measured and recorded during patient encounters. BMI (kg/m^2) values may be obtained either directly from EMR systems or may be calculated from synchronous height and weight values. The process of BMI calculation and cleaning specifically for this study included exclusion of calculated BMI less than 15 and larger than 50 kg/m^2; as we assumed that these values were most likely erroneous. If a patient had multiple BMI values on the same day, only the first value was selected for the analysis. BMI was categorised as underweight (BMI ≤ 20 kg/m^2), normal weight (20 < BMI ≤ 25), overweight (25 < BMI ≤ 30), and obese (BMI > 30).

Covariates and confounding

Sex, age, rurality status (base on rural/urban postal code), deprivation index (calculated using 6-digit postal codes), history of smoking (past or current smokers versus non-smokers) and comorbidity index (defined as the number of chronic diseases with validated CPCSSN case definitions (hypertension, diabetes mellitus,

osteoarthritis, depression, epilepsy, chronic obstructive pulmonary disease (COPD), and Parkinson's disease) with evidence of obesity as a causal risk factor were adjusted for in the analysis.

Statistical analysis

Descriptive analysis compared demographic and baseline health characteristics, as well as baseline BMI readings of cases and controls, using *t*-test for continuous variables and chi-square test for categorical variables. Analysis 1 included inferential statistics using Cox's proportional hazard to produce hazard ratio estimates; BMI was included as a predictor in Cox's models in two forms, as a continuous and categorical variable. Analysis 2 included unconditional logistic regression to estimate odds ratios of dementia onset between people with and without a dementia diagnosis using BMI measured before and after the index dates, as well as changes in BMI before and after diagnosis (13). Median BMIs were used to avoid using only the single most recently recorded BMI which might produce misclassification bias. Age at baseline, sex, and number of comorbidities were also included as covariates since matching on these variables may have produced bias as people with dementia are more likely to be older and female (14). Assumptions of proportional hazard over time-at-risk for Cox's regression were checked using log-minus-log (LML) plots. Linearity was checked for continuous variables using its categorical form. SQLite (15) was used for data management and STATA 14 (16) was used for data analysis.

Ethics

The CPCSSN database has received general ethics approval from each contributing network's host university's Research Ethics Board, including waivers of individual patient consent for their de-identified data to be used for surveillance and research. This study also received specific approval from the Research Ethics Board at the University of Alberta (Pro00083659).

RESULTS

Among 39,066 eligible patients, 26,878 (69%) had at least one BMI value before or during the follow-up period, while 12,090 (31%) had at least one BMI and 6,390 (16%) has at least two BMI values up to five years before baseline (from 2004 to 2008). Eligible people with two or more BMI values were slightly younger, more likely to have urban postal codes, a record of smoking at any point in time and at least two chronic diseases with valid CPCSSN case definitions ($p < 0.001$). However, the differences in distribution between compared groups were small (less than 10% for all cases).

Among 6,390 people with at least two BMI values up to five years before baseline (analysis 1), the number of new cases of dementia in 2009-2017 was 784 (12.3%). People with dementia were older, more likely to live in a postal code area with a higher social deprivation index value (more deprived) and more likely to have two or more chronic diseases, but the differences were not statistically significant. Table 4-1 presents baseline demographic and relevant clinical characteristics with comparison between people who developed and did not develop dementia for the cohort of eligible patients as well as for the cohort used for analysis 1.

Analysis 1 estimated the risk of incident dementia diagnosis for each one unit increase in BMI before baseline. Different methods of inclusion of patients' BMIs, including the most recent BMI before baseline, median and mean of all BMI values within the time range, were analysed. No difference was found between mean and median BMIs. This study reports results using the median of all recorded BMIs during five years before baseline. For people aged 65-79 with two or more BMI values the HR was 0.99 (95%CI, 0.98-1.01, p-value = 0.052) after adjusting for age, sex, postal code, deprivation categories, smoking history, and comorbidity index. For the older than 79 years old group the adjusted HR was 0.94 (95% CI, 0.94-0.99, p-value = 0.019). For every 5-unit increase in BMI, HR = 0.97 (95% CI, 0.88-1.06) and 0.84 (95% CI, 0.72-0.970), p-value = 0.052 and 0.019, respectively

for the two groups. Table 4-2 presents results from Cox's survival analysis using BMI as a continuous variable.

A Cox's survival analysis of the association between BMI and weight, treating BMI as a categorical variable. Among people aged 65-79y, HR = 1.34 (95% CI, 0.78-2.36, p-value = 0.283), 0.98 (95% CI, 0.79-1.22, p-value = 0.859), and 0.98 (95% CI, 0.77-1.25, p-value = 0.876), respectively when comparing risk between normal, underweight, overweight, and obese people. Among people aged 80 and older, HR = 1.71 (95% CI, 0.98-3.00, p-value = 0.060), 0.75 (95% CI, 0.56-1.01, p-value = 0.057), and 0.78 (95% CI, 0.55-1.01, p-value = 0.165). Results are included in table 4-3.

Analysis 2 compared the BMIs of matched-paired cases and controls for the time before and after index dates. The number of case and control sets who had at least two BMIs before and two BMIs after an index date was 726 (726 cases and 2,904 controls). During the follow-up period before the index dates, people with lower BMIs are more likely to be diagnosed with dementia, BMI difference was about 0.7 kg/m^2, p-value = 0.001; this number for the period after index dates was 1.1 kg/m2, p-value < 0.001. Taking the median of all BMI values before index dates, the OR = 0.97 (95% CI, 0.95-0.99, p-value = 0.001); while OR = 0.96 (95% CI, 0.94-0.97, p-value < 0.001) for BMI after index dates (Table 4-4).

The BMI of people with an incident dementia diagnosis decreased more than those people without this diagnosis (p < 0.001). The difference in BMI between the two groups of people was about 0.4 kg/m^2. Taking the median of differences in BMIs before and after index dates to compare between cases and controls, people who lost more weight are more likely to develop dementia during follow-up, OR = 0.91 (95% CI, 0.88-0.95, p-value < 0.001) (Table 4-4).

DICUSSION

A common belief about the association between BMI and chronic diseases, including dementia, is that people with higher BMI, especially those who are overweight or obese, are at higher risk of subsequent comorbidities (17). However, there is evidence that overweight and obese people might be protected against dementia onset (1, 18).

This study found that among very old community-dwelling adults (people aged 80 and older), each one-unit increase in BMI recorded within five years prior to baseline was significantly associated with a reduction of 3% in risk for dementia onset during the next 10 years. In this study, on average, an older adult had a 16% lower risk for incident dementia for each 5-extra-unit of BMI or, in other words, by moving up from one BMI category to the next. Consistent with this finding, a meta-analysis using data from Europe, the United States, and Asia found a reduction of 29% in risk of dementia (95% CI, 0.66-0.77) for every 5-unit rise in BMI during the 10 years preceding an eventual dementia diagnosis (19). However, as the association between BMI and dementia onset does not appear to be linear (figure 2), we categorized BMI into four groups of under, normal, overweight, and obese and found that being underweight was not statistically significantly associated with an increased risk at significant level of 0.001 (p-value = 0.04); while being overweight and obese was associated with a relatively and non-significantly lower risk, compared with the risk among normal weight patients. This could be interpreted that the strong negative effect of being underweight on dementia risk has overcompensated for the effect on the association between BMI in dementia and general.

From the nested-matched-paired case-control study both cases and controls experienced a statistically significant reduction in BMI over time; people with lower BMIs and lost more weight are more likely to be diagnosed with dementia. So, a falling BMI may be an early sign of dementia onset. This trend seems to continue after diagnosis. Even though weight loss before dementia diagnosis has been

reported by a number of previous studies, to our knowledge, it has not been compared to people of the same age without a dementia diagnosis. There is existing evidence for lower weight before diagnosis among overweight and obese people, but not in those who are underweight or of normal weight, and with a stable BMI after diagnosis (20), although the main outcome in the mentioned study was Alzheimer's disease rather than dementia in all its sub-types. This study observed that people with dementia had lower BMI before and after index dates, by 0.5 and 1.1 kg/m2, respectively. And after being diagnosed with dementia, cases lost significantly more weight than people in control group, by 0.36 kg/m^2.

This finding of weight loss among older adults could possibly be argued as being a part of the natural aging process as lean muscle is lost replaced by fat, which has lighter density (21). Taken together, this may raise a question of whether people with dementia, including those in its pre-clinical stage, are more likely to have lower, apparently "healthier" BMIs; as taking less exercise and poor diet contributes to weight loss. Such weight loss may also reflect the onset of frailty in dementia which has such a lengthy latent period. Additionally, the loss of height among older adults, particularly in women needs to be considered when calculating BMI. While waiting for future clinical studies to focus on lean mass loss to test this hypothesis, this study suggests that gradually losing weight among what appears to be physically healthy people may be an indicator for early dementia screening.

Even though there are arguments against using body mass index (BMI) as a principal indicator for obesity since it may not reflect the true body fat proportion, it is still one of the most comprehensive sources of data for its ease of measurement, which reduces potential for errors, as well as its ubiquitous availability in most medical record systems (22); it also appears to be well recorded in electronic primary care data (23). Good use of BMI data could benefit both researchers and practitioners in order to predict risk of multiple chronic disease development, including dementia. However, using only one BMI measurement at the point most

recent to baseline might be subjected to systematic errors. Instead, the use of mean or median BMI may be more appropriate in order to reduce information bias. Ideally, I believe that this association should be studied using time-series methods to capture the actual change in BMI in years before and after a dementia diagnosis. In the meantime, CPCSSN data is not capable for this type of analysis yet.

The association of BMI lower or higher than the normal range and a higher risk of dementia onset is clearer in studies in younger people (those aged less than 60 at baseline) and with 10 or more years of follow-up (24). A replication of this study in future, when CPCSSN has a longer time series of data, may reveal a clearer result.

CONCLUSION

Overall, this study did not find a statistically significant association between BMI before baseline and dementia onset. However, it provides evidence that older adults commonly lose weight, and that people diagnosed with dementia are more likely to weigh less before that diagnosis and are more likely to lose more weight afterwards than those who have not been diagnosed with the disease. Thus, in a same age range, community-dwelling older adults with higher BMI have a lower risk of subsequent dementia. Therefore, though still in need of further exploration, primary care monitoring BMI in seniors may help to identify dementia earlier than is currently achieved. This may form the basis of a reference for family medicine and public health in order to plan a treatment strategy for people in need. In addition, this study also showed that secondary use of health data from electronic medical records should consider using BMI data as a valuable and readily available resource.

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Figure 4-1. Flowchart of cohort identification

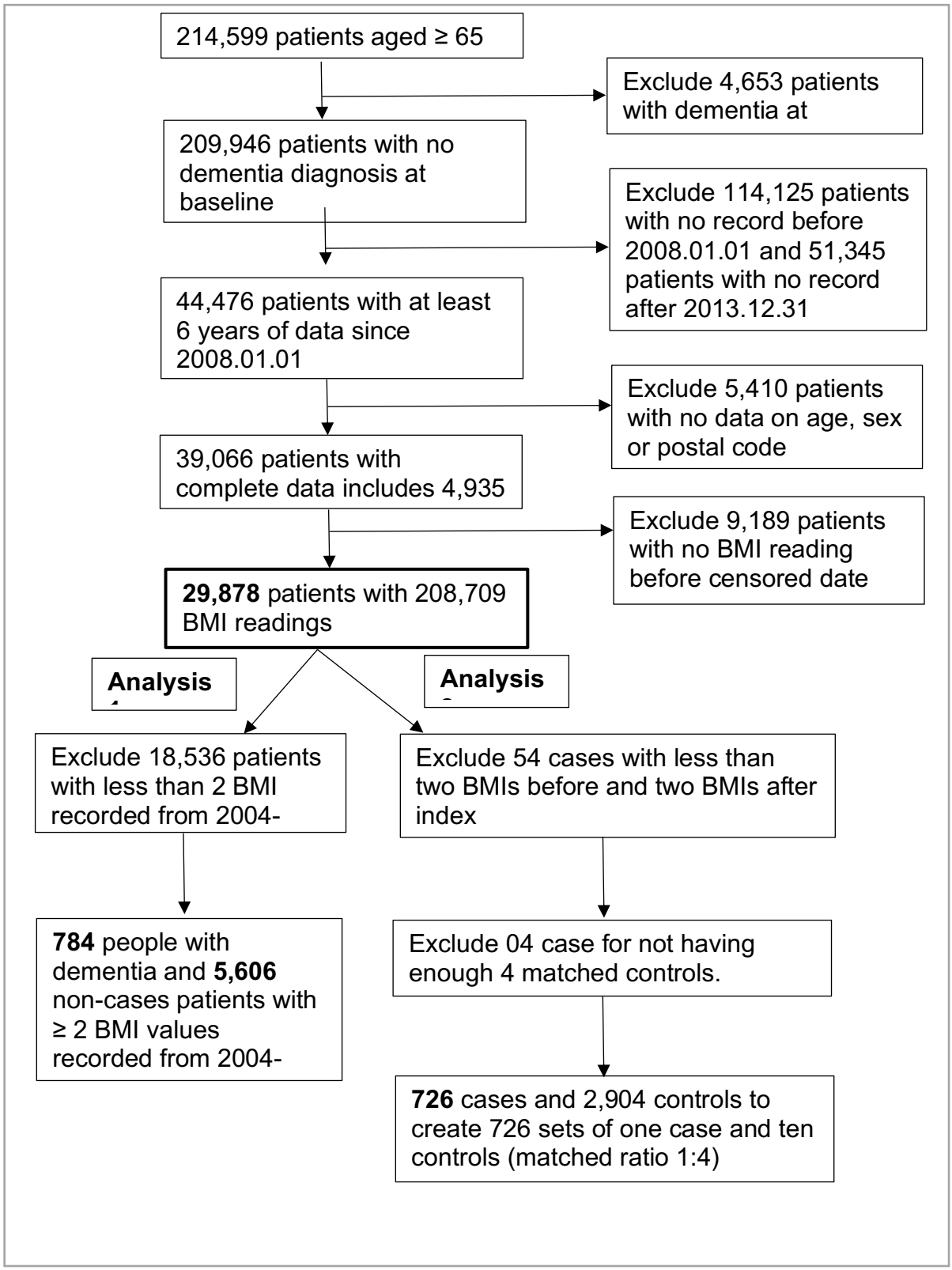
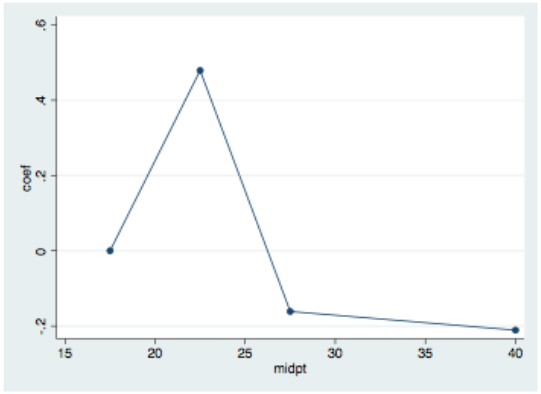
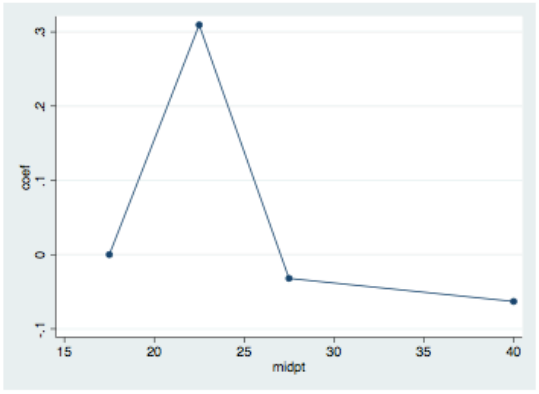


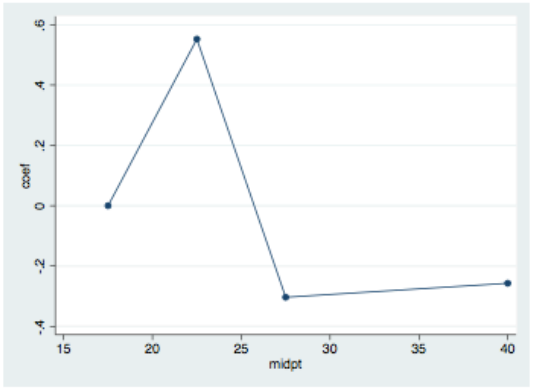
Figure 4-2. Checking linearity of BMI effect on dementia onset



All cohort



Younger group



Older Group

Table 4-1. Demographic and clinical characteristics of cases and non-cases at baseline

	Whole cohort			People with two or more BMI values before baseline		
Variable	**Non-cases n = 34,132**	**Cases n = 4,935**	**Total n = 39,067**	**Non-cases n = 5,606**	**Cases n = 784**	**Total n = 6,390**
Age (mean (SD))	73.6 (6.1)	77.8 (6.5)	74.1 (6.2)	73.0 (5.6)	76.7 (6.1)	73.5 (5.8)
Female (n (%))	19,528 (57.2)	2,957 (59.9)	22,485 (57.6)	3,255 (58.1)	456 (58.2)	3,711 (58.1)
Urban (n (%))	25,799 (75.6)	3,900 (79.0)	29,699 (76.0)	4,622 (82.5)	677 (86.4)	5,299 (83.0)
Smokers (n (%))	8,790 (25.8)	1,252 (25.4)	10,042 (25.7)	1,710 (30.5)	255 (32.5)	1,965 (30.8)
Deprivation index						
Social Quintile 1	5,247 (15.4)	606 (12.3)	5,853 (15.0)	838 (15.0)	84 (10.7)	922 (14.4)
2	8,208 (24.1)	1,007 (20.4)	9,215 (23.6)	1,016 (18.1)	142 (18.1)	1,158 (18.1)
3	7,152 (21.0)	1,079 (21.9)	8,231 (21.1)	1,238 (22.1)	169 (21.6)	1,407 (22.0)
4	5,948 (17.4)	971 (19.7)	6,919 (17.7)	1,336 (23.8)	194 (24.7)	1,530 (23.9)
5 (most deprived)	7,577 (22.2)	1,272 (25.8)	8,849 (22.7)	1,178 (21.0)	195 (24.9)	1,373 (21.5)
Material Quintile 1	7,151 (21.0)	1,163 (23.6)	8,314 (21.3)	1,582 (28.2)	243 (31.0)	1,825 (28.6)

2	5,703 (16.7)	799 (16.2)	6,502 (16.6)	1,273 (22.7)	178 (22.7)	1,451 (22.7)
3	5,969 (17.4)	809 (16.4)	6,778 (17.4)	1,164 (20.8)	109 (13.9)	1,273 (19.9)
4	8,000 (23.5)	1,189 (24.1)	9,189 (23.5)	811 (14.5)	135 (17.2)	946 (14.8)
5 (most deprived)	7,309 (21.4)	975 (19.8)	8,284 (21.2)	776 (13.8)	119 (15.2)	895 (14.0)
Comorbidities						
0	15,921 (46.7)	2,082 (42.2)	18,003 (46.1)	2,183 (38.9)	276 (35.2)	2,459 (38.5)
1	12,025 (35.2)	1,702 (34.5)	13,727 (35.1)	2,207 (39.4)	307 (39.2)	2,514 (39.3)
2	4,867 (14.3)	862 (17.5)	5,729 (14.7)	943 (16.8)	147 (18.8)	1,090 (17.1)
3+	1,319 (3.9)	289 (5.9)	1,608 (4.1)	273 (4.9)	54 (6.9)	327 (5.1)

Table 4-2. Adjusted hazard ratio of dementia onset using BMI values within five years before baseline (Analysis 1)

		65-79 years old		80+ years old	
Median BMI	Mean (SD)	AHR [95% CI]	*p*-value	AHR [95% CI]	*p*-value
1-unit increment	28.2 (4.9)	0.99 [0.98-1.01]	0.502	0.97 [0.94-0.99]	0.019
5-unit increment		0.97 [0.88-1.06]	0.502	0.84 [0.72-0.97]	0.019

* AHR: Adjusted hazard ratio: Survival Cox's models include age at baseline, sex, FSA, deprivation index, history of smoking and number of comorbidities as covariates

Table 4-3. Adjusted hazard ratio of dementia onset using BMI as a categorical variable

	All cohort		65-79 years old		80+ years old	
BMI	AHR* [95% CI]	p-value	AHR* [95% CI]	p-value	AHR* [95% CI]	p-value
Normal weight	1.00	--	1.00	--	1.00	--
Underweight	1.50 [1.02-2.22]	0.040	1.34 [0.78-2.36]	0.283	1.71 [0.98-3.00]	0.060
Overweight	0.89 [0.75-1.07]	0.214	0.98 [0.79-1.22]	0.859	0.75 [0.56-1.01]	0.057
Obese	0.91 [0.75-1.11]	0.348	0.98 [0.77-1.25]	0.876	0.78 [0.55-1.01]	0.165

* AHR: Adjusted hazard ratio: Survival Cox's models include age at baseline, sex, FSA, deprivation index, history of smoking and number of comorbidities as covariates

Table 4-4. Comparing BMI before and after index date of people with and without dementia onset (Analysis 2)

	Cases	**Controls**	**AOR***	**p-value**
Before Index Date	Mean (SD)	Mean (SD)		
Median BMI	27.2 (4.7)	27.9 (4.8)	0.97 [0.95-0.99]	0.001
After Index Date				
Median BMI	26.6 (4.7)	27.7 (5.0)	0.96 [0.94-0.97]	< 0.001
Difference in BMI	-0.59 (2.3)	-0.23 (2.0)	0.91 [0.88-0.95]	< 0.001

* AOR: Adjusted odds ratio: unconditional logistic models include age group at baseline, sex, FSA, deprivation index, history of smoking

CHAPTER 5. DISCUSSION AND CONCLUSION

Recent evidence shows a decrease in the age and sex adjusted incidence of dementia in some populations, which may be due to higher education levels, improved socioeconomic conditions, and better control over cardiovascular risk (1). However, as populations age, the prevalence of dementia will still increase. As of 2015 worldwide, there were 47 million people living with dementia, and this number is expected to nearly double by 2030 (2). In 2016, 564,000 Canadians were living with dementia with about 25,000 new cases diagnosed every year, it is predicted that by 2030 almost 1 million Canadians will be living with a dementia (3). In this country there has been little research on risk factors for dementia in primary care despite the fact that dementia is commonly first diagnosed in that setting, from which substantial risk and morbidity data are available.

This thesis reports on the epidemiology of dementia in community-dwelling Canadian older adults (chapter 3), potential relationships between dementia onset and cardiovascular disease risk factors as well as other chronic diseases (chapter 4), and a sub-analysis of how BMI affects the risk of dementia development (chapter 5). Previous population-based studies using primary care or national insurance administrative data on dementia onset and its risk factors have been conducted in the United Kingdom (4, 5), Taiwan (6, 7), and South Korea (8), where health care systems are universal with similar characteristics to that in Canada. The methods of collecting and analyzing data presented in this thesis have been adapted from these studies with modifications to avoid previously made errors or bias, and to fit the available CPCSSN data.

Incidence of dementia diagnosis consistently increased over the period 2009-2017. The nine-year incidence rate was 15.0 cases per 1,000 person-years with increased rates associated with higher patient age.

Age and sex as risk factors for dementia have been relatively well-explored over the past few decades. According to a Public Health Agency of Canada report (9) and recent findings from the Chicago Health and Aging Population Study (10) and the Framingham Heart Study (11), the risk of dementia onset accelerates as people get older. This study demonstrated the same trend. Here, the incidence rate changed from 0.8 cases per 1,000 person-years in people aged 65-69 to 7.5 cases per 1,000 person-years in people aged 90 and older. The rate met its peak for those 90-95 years old, then declined to 4.8 cases per 1,000 person-years among people aged 95 and over. This may reflect mortality as a competing risk, with people in poorer health and having a higher risk of developing dementia dying before the age of 90-95y.

Contrary to some other studies (12, 13), I found that in the same five-year age ranges, people who were born in later years were estimated to be at higher risk of dementia developing. I also found that annual incidence rates in rural areas are significantly lower than in urban locations. This may be explained by patients' lower level of awareness and willingness to be diagnosed or even recognition of dementia as an entity; lower rates of higher number of patients per health care providers, especially physicians with experience in geriatrics and dementia in rural neighborhoods might also makes the rate of underdiagnosis higher in rural areas (14).

In general, my findings reflected an expected trend; that as the general population achieves longer life expectancy, the number of people who are going to live with dementia and require health support is increasing. In this aging population, as more and more people live to be 80 or 90 years-old, it is expected that prevalence, incidence and burden of dementia will continue to increase at least for the next few decades (15). The increasing number of recognized cases in community dwelling persons in developed countries at least, may lead to improvement of dementia awareness among primary care providers as well as amongst patients and their families (15) leading eventually to overall reduction in risk. This, combined with a

possible post-baby boom reduction in the proportion of elderly citizens in the general population, may also lead to a lowering of dementia prevalence.

Chapter 4 examines associations between selected risk factors and the incidence of dementia. As expected, a history of depression consistently increases the risk at all ages which aligns with the results of a recent meta-analysis of eighteen studies worldwide (16). Depression may be a prodrome of dementia in which older adults with depression develop symptoms of dementia like memory loss or personality changes (17) or the two diseases are co-occurred as they share common risk factors (18). However, the association between dementia and depression is complicated and as yet clearly unknown with regards to their etiological connections (19). It may also be that depression is a consequence of dementia symptoms that affect patients' during the latency period for dementia (20).

Residence in socially deprived neighbourhoods, osteoarthritis and diabetes mellitus people at younger age (65-79 years old) is associated with a higher risk of dementia, while residence in materially deprived neighbourhoods decreases the risk for people at older age (80 and over years old). Socially deprived neighbourhoods report higher rates of separated, divorced or widowed residents, implying more people living alone, or who have moved home more often, and are at higher risk than those who lived in more stable neighbourhoods. It is unknown to what extent people 80y-and-older who live in neighbourhoods with lower household income, higher unemployment, and lower educational attainment are also at lower risk of dementia, but I suspect that there is likely to be higher rate of undiagnosed dementia in these neighbourhoods. Hypertension, obesity and dyslipidemia recorded in primary care do not significantly predict dementia onset. This might be because blood pressure levels of hypertensive patients mostly return to normal following clinical recognition and management, which ceases the damage to organs and systems, including the cardiovascular and nervous systems. Unlike findings from a recent meta-analysis (21), the use of anti-

hypertensive medication did not show a significant association as also has been seen in previous studies (22). However, it is interesting to see no effects on dementia incidence caused by dyslipidemia and obesity. Literature on these two factors remains controversial with no strong evidence for an association in either direction (23). I have been unable to identify any systematic review or meta-analysis on the association between dyslipidemia and dementia. Evidence for a protective effect of obesity against dementia developing has been reported (24) while some others have suggested looking into weight changes and BMI trajectories to obtain a clearer view about this association, especially during the early stage of dementias (25-27).

The analysis used in chapter 4 examines the effects of risk factors on incidence of dementia using dichotomous variables for all predictors to utilize the advantage of recorded health data, assuming people who have not been diagnosed with a chronic disease at a specific time are free from that disease up to that point. Analysis using routinely collected data has an advantage of holding a relatively large sample size which should be representative of the general population. However, an important disadvantage of using these data is that they were not collected for any specific research purpose; therefore, missing data are common and the data loss due to loss to follow-up. Data input accuracy may be very high if strict inclusion and exclusion criteria, as normally done within a randomized controlled trial or other traditional research designs, are applied. For example, patients may have all required data except blood pressure values, which makes them ineligible to be included in an analysis using blood pressure as a continuous variable to predict an outcome. However, as we search through their charts, we may find that they have never been prescribed with an antihypertensive, and never been recorded as having a diagnosis of hypertension. This makes it likely that these patients do not have hypertension, and if we use hypertension as a binary variable in our analysis, we could possibly include them. Further, this approach is pragmatic as blood pressure is subject to change according to specific situations.

As this is an exploratory analysis, it is preferred to include as many people as possible and to minimize the exclusion of patients, thereby reducing selection bias.

After looking into potential factors associated with dementia onset, and in light of previous studies' examining the relationship between BMI and incidence of dementia, I undertook a *post hoc* analysis on a sub-cohort with higher precision estimating the association between BMI and incidence of dementia, presented in chapter 5. This included only eligible participants from the analysis described in chapter 4, but with an additional inclusion criterion: patients had to have at least two BMI measurements between 2004 to 2009 inclusive (five years before baseline) to further explore the association between BMI recorded in later life and subsequent risk of dementia. BMI as a predictor was also included in analysis models in two forms: as a continuous variable and a categorical (four-part) variable (using the World Health Organization case definition for obesity). As a continuous variable, an increase of one unit in BMI was associated with a 3% higher risk of a dementia diagnosis. However, this association is not linear, with a sharp positive trend among people with BMI lower than 20kg/m^2, followed by an as sharp negative association among people with BMI 20-25kg/m^2, then a rather moderately negative association for BMI above 25kg/m^2. There was a significant association between being underweight and 50 % higher risk of incident dementia for people at all ages ($p = 0.040$); overweight and obese people experienced a lower risk of 11% and 9% in comparison to people at normal weight, though the strength of these two associations did not reach statistical significance. In general, there was no significant association between categorical BMI and the risk of dementia development. However, when looking into weight changes before and after a diagnosis of dementia in primary care, even though patients in both groups (that is, cases and non-cases) declined in weight over time, for each one unit increase in BMI before and after index dates the odds (risk) of dementia onset statistically significantly decreased by about 3% and 4% respectively. Comparing weight loss before and after a diagnosis, a one unit increase in BMI also statistically significantly decreased the risk by 9%. This is consistent with the level of findings

from the whole cohort. However, these figures should be cautiously interpreted, for it might be erroneous to conclude a protective effect of being obese in respect of dementia onset. Rather, it is more likely the effect of a highly positive association between being underweight and dementia onset that produces such a result in the continuous data (28). One argument should also potentially be considered is that even though the decrement is statistically significant, it may not be clinically relevant for the reason that the number of cases included is relatively large. People with a diagnosis of dementia have a significantly lower BMI than people without it, which indicates a known trend of losing weight among cognitive impaired patients which occurs perhaps years before a clinical diagnosis (29). This is explained by a number of reasons; for example, reducing food intake including forgetting to eat or losing appetite (30) or changes in social and physical function, although a clear mechanism behind this phenomenon remains to be elucidated (31).

Nevertheless, a practical application for this finding may be to reinforce the utility of continual weight measurement for all mid-to-late age patients in primary care, with the purpose of early identification of people who will become diagnosed with any type of cognitive decline later. This may give an opportunity to consider relevant care, education and support for patient and caregivers substantially ahead of a diagnosis, rather than reactively later (16). For instance, older adults who are seen to be gradually losing weight over the course of a year or two may be recommended to undergo office-based dementia screening, which might include informal interviews with patients and their families, as well as a short cognitive questionnaire such as the MMSE (32), the clock-drawing test (33) or the MoCA (34). Such screening has been discussed in the 2019 report by the American Alzheimer's Association (15) and are low-cost, low time-consuming but effective at community level.

Implications for policy

The Canadian incidence rates for dementia are predicted to continue to increase, reaching a million people by 2030 (35). Excluding Canada, thirty-one countries

worldwide have developed and employed a national strategy. With the Canadian National Strategy published last year (35), higher incidence rates in the near future are predictable as awareness increases among health care providers, people at high risk and their family members. However, my finding suggesting slower increment among the oldest old, which aligns with current evidence (36), suggests that the predicted longer term burden on society may be being overestimated. Also, as my study found that some common risk factors were not associated with dementia among people aged 80 and older, there may be a need to employ a different approach to identify high risk groups among these oldest old (4). For example, instead of hypertension, diabetes, being overweight and obese being concerns, low cholesterol levels, hypotension, low blood sugar and being underweight may be of concern in association with the effects of general frailty. Policymakers may be advised to identify and distinguish these high-risk groups, with different needs and levels of need, to appropriately adjust and reallocate health resources.

Investment and encouragement in developing a risk score to predict dementia onset, similar to that developed in the UK by Walters and colleagues using primary care data (4) but with adjustment to accommodate data availability in that Canada, should be considered to support primary care providers in improving timely dementia diagnosis and identifying people at low as well as those at high risk of dementia, in order to more effectively target dementia screening.

While it may be argued that to know or not to know about the existence of the disease in earlier stages may constitute a moral dilemma since there is no known cure and it might cause unnecessary worry, eighty percent of older adults believe that they need regular cognitive checks (37) and ninety-five percent of primary care patients and their families who have been asked do wish to know if they have dementia (38). Patients also showed willingness to be diagnosed by their family physicians, especially those by whom they have been treated by for a substantial amount of time, as it is more comfortable and secure to have this type of discussion

with those with whom they are familiar (37, 39). This supports encouragement of future related research in primary care settings to provide more evidence and equipment for family physicians in order to accurately diagnose and manage dementia in a timely fashion. For irreversible dementias, patients may have a chance to be treated with cholinesterase inhibitor medication. Even though benefits of using of them during mild to moderate stage are small (40, 41).

From the public health perspective, early diagnosis is essential for health policy and strategic planning (42), which should include guidelines for routine check-ups among people at higher dementia risk (e.g. people who have diabetes mellitus) or people who may have early signs (e.g. people who lose weight over time), and guidelines for brief cognitive assessment. However, as a diagnosis of dementia without sufficient knowledge and support being provided may cause frustration and lead to more harm than benefit, guidelines for how to give the diagnosis without causing too much fear and anxiety, that is to balance benefits and potential negative impacts of being diagnosed on people with dementia and their families' life should be widely applied (39). In order to further encourage early diagnosis of dementia in primary care settings, there should be activities to enhance awareness about the condition, and to differentiate the changes of dementia from those associated with normal aging. Further research on dementia epidemiology and management in primary care should be encouraged; there should be more effort to translate knowledge learnt from research not only to primary care providers and policy makers but also social workers and, especially, the general population.

Strength and limitations

The Canadian primary care system is not only the first point of care for most people in the community but also a place where continuity of care fosters patients' trust in their health care providers and where they feel most comfortable to share their health problems. As about half of a family physician's patients are estimated as being people living with chronic disease, data from primary care settings are ideal for studying diseases with a long latency period such as dementia.

The CPCSSN is a system that records clinical primary care data, extracted from individual EMRs held by family physicians and other primary care providers across the country (43). Data on hospital-based acute care, or care provided in long-term institutions, are typically not contained in the primary care EMR (44). Briefly, CPCSSN data includes patient-level information for diagnosis, prescribed medications, demographics (age, sex, postcode of residence, deprivation index), height and weight, referrals, co-morbidity and risk factors. From 2008, CPCSSN has had reliable data that can be used to investigate the incidence, prevalence, and management of various diseases in primary care. CPCSSN extracts de-identified clinical information from EMRs in eight provinces and territories, standardizes the data, and stores them in a high security environment. The data are available for research and quality improvement initiatives. The CPCSSN currently includes more than 1.9 million patients from twelve networks across Canada. CPCSSN provides a unique opportunity to observe and analyze the occurrence of chronic diseases over time in Canadian primary care users. Utilizing CPCSSN data, it is possible to (1) calculate incidence rates and prevalence; and (2) identify affected groups of persons at high and highest risk.

The main advantages of using routinely collected population-based data are its low cost and availability, with significant benefits of a cohort design in which a large sample with comprehensive information will noticeably increase the precision of outcome estimates. Having a large and ready-to-use sample like that from CPCSSN reduces financial, human, and other costs, especially when dementia (the outcome) is considered a fairly common chronic disease but with a long latency period. One noteworthy advantage is that data are collected prospectively and systematically by practitioners, which should minimize information bias (45).

In regards to the design of this study, a retrospective cohort study is a longitudinal observational study in which participants are free of disease (or other outcome of interest) at baseline and are divided into two or more groups with or without

exposure to one or more potential risk factors. In this study, the study population only includes people free of dementia at baseline with one run-in year, which is expected to allow accurate identification of incident cases. It is also efficient to conduct a retrospective cohort rather than a prospective one. Most importantly, as both exposed and unexposed cohorts are believed free from dementia at baseline, the sequence of health conditions onset and outcomes will be recorded, which allows a direct approach for new evidence on potential causal relationships. Further, implementing a dementia-free cohort also allows for a highly precise denominator for incidence rate calculation and survival analysis.

On the other hand, it is acknowledged that some exposures to risk factors are subject to change during follow-up, which may lead to misclassification bias. However, patients' health conditions in the CPCSSN are usually monitored reasonably closely. For potentially modifiable variables like body mass index, medians of all eligibly available values recorded within a specific period of time were estimated.

Another major concern about longitudinal studies in older people is selection bias due to loss to follow-up and attrition. This could make measuring risk of disease impossible. However, by setting a criterion of having at least six years of data and by adjusting for age in all statistical models, the effects of missing cases and inaccurately recorded data have been minimized.

In addition, competing risks attributed to other possible factors include inherited genetic conditions, educational level, and physical inactivity. It is not possible to account for these effects because these variables are rarely recorded in primary care electronic medical records. Competing risks deriving from the presence of comorbidities other than that included in the analyses may also be present but are unknown. Linkage of primary care data, hospitalization data and administrative data, including death certificate data, is planned for future exploration of risk and protective factors for the incidence of dementia.

Another potential bias is misclassification bias as diseases may have been unrecognized by the definitional algorithms that have been used to detect cases. Thus, cases may be flagged as non-cases. Diseases with validated CPCSSN case definitions (For example, dementia, hypertension, and diabetes mellitus), are still subject to misclassification because none of them has 100% sensitivity, specificity, PPV and NPV (46). The CPCSSN dementia case definition has a sensitivity of 96.8%, which means that in 100 people with a 'true' dementia diagnosis, only about 97 of them meet the CPCSSN criteria to be defined as cases. This discrepancy is an expected feature of secondary data use. Misclassification bias might also happen under immortal time bias as patients may have been classified as non-dementia during the latent period of the disease.

Furthermore, not all dementia cases are diagnosed by primary care providers, and, as the very old are more likely to move to nursing homes or long-term care institutions, a number of people may be lost to follow-up before becoming an incident case. For example, there are 8,130 out of 39,066 (20.8%) patients in this cohort having exit dates before the last year of follow-up (2017). However, a criterion of having at least six years of data was set from the beginning to ensure as much time as feasible for dementia to be observed. Also, as the target population for this study was community-dwelling seniors, dementia cases diagnosed while resident elsewhere were outside its scope.

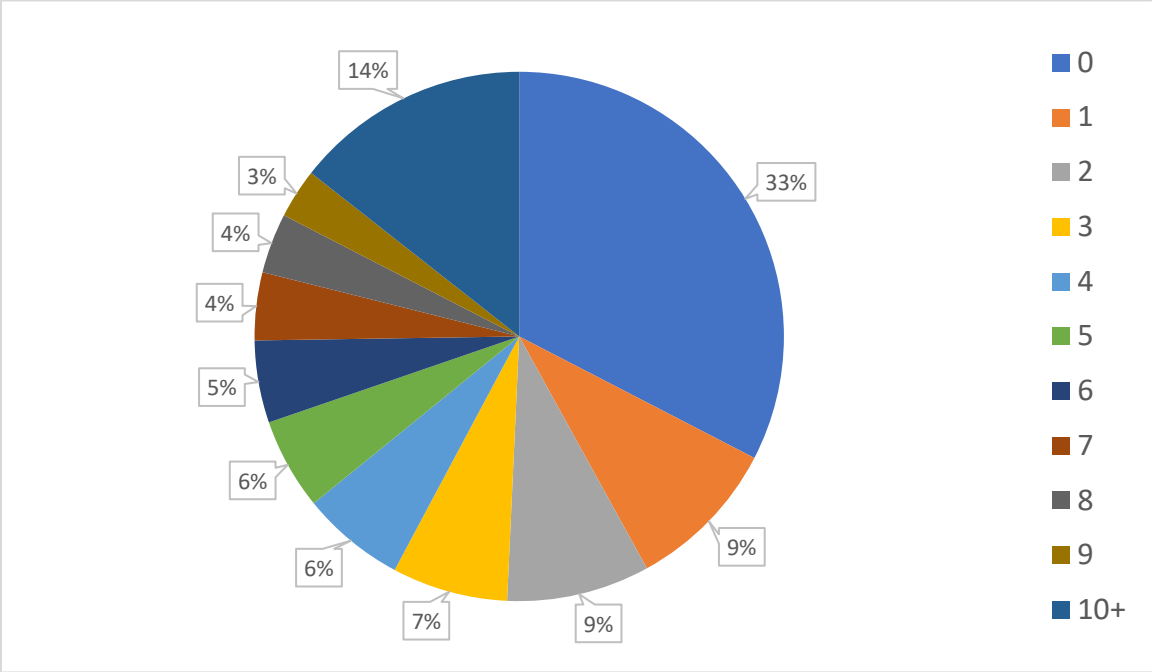
In term of data completeness, it is believed that BMI data recorded in EMR is richer, more accurate and therefore more reliable than other resources like national surveys or self-reports (47). It is true that there is evidence that weight and height data are not missing-at-random: patients who are at normal weight are less likely to have their weight measured than those who are overweight or obese, while younger patients and those without chronic diseases are also less likely to have their weight and height measured than patients who are older or more medically complex (48). However, completeness of BMI data in primary care has been

impressively improving over the years; the prevalence of obesity in CPCSSN data is comparable with that in other national databases, while the prevalence of being underweight is about three times higher (49). It is not known yet if existing missing BMI data are due to it not being measured or recorded, or whether it is recorded in data fields in the electronic medical charts which are not being coded and used by entities like CPCSSN. Future investigation is required to further improve data quality. In the analysis in this study, comparing BMI of people with and without dementia, there was no difference in the frequency of BMI measurement between people with dementia and those not diagnosed with the disease no obvious selection bias was identified.

As an example of the secondary use of data collected for clinical rather than research purposes, problems with the data, including its completeness, are almost inevitable. Even though routinely measuring height and weight at every primary care visit was recommended more than a decade ago for its clear benefit in recognizing and monitoring obesity (50), it is not universal practice in Canadian family practice. Among 44,476 patients aged 65 and older who were free from dementia in 2008 forward, 33% had no BMI measurement recorded over a mean of 13 years of follow-up (SD = ± 3.8); more details on the proportion of CPCSSN data by number of BMI measurements recorded are included in the graph below:

On the other end of the weight scale, older adults with low BMI are also at higher risk of many chronic diseases and mortality (51, 52) yet they are not often targeted to have weight and height measured (49). Though likely to be an underestimation, the CPCSSN database has approximately triple the proportion of underweight patients in comparison to national surveys like the Canadian Community Health Survey (CCHS) and the Canadian Health Measures Survey (CHMS) (49), which makes it a very good source for studying the U-shape distribution between BMI and chronic diseases.

Figure 5-1. Count of BMI records in national database from 1990 to 2017



Missing data attributable to being intentionally unrecorded in the EMR

In the 2017 dataset used for my study, the proportion of 'missing' data in CPCSSN remains relatively high. For example, among all CPCSSN patients aged 65y and older, weight is documented in 51%, height is documented in 43%, and BMI was recorded and/or calculated for only 41%. In my cohort, including only patients with age, sex, FSA, and at least six years of record, I was able to identify BMI for 68% of participants.

Since CPCSSN data are collected during clinical encounters between patients and providers using a system designed to support patient care and not for research, a concern about data being missing is to determine whether absent data are truly missing or never existed. Data which are truly missing must have once existed and been recorded but later become lost from the record, or be present in the record but not extracted from it, or be existent but intentionally not recorded, possibly because they are judged to be clinically uninformative.

Examples of the latter include family physicians judging it unnecessary to spend time measuring and recording the weight of a patient who ‘looks’ to be of normal weight and appears not to suffer any significant disease burden; or they may not weigh their patients at every visit if they ‘look’ the same as in previous encounters, which would render a single weight or BMI value clinically applicable over a subsequent period of time.

A similar scenario may apply to smoking, alcohol consumption, personal medical history, family history, and other variables. The phenomena are certainly extant, but data which represents them in the record may be absent because the attending service provider believed that the information was uninformative. Furthermore, information recording absence of a condition, like ‘no history of depression’ or ‘non-smoker’, may be unrecorded and the field left blank because the physician's recording rule is to denote extant conditions, not absent ones. Each of these types of missingness may derive from providers not having purpose in recording the existence and nonexistence of conditions. But such absences in the clinical data may still be coded as ‘missing’ in the analysis because amongst analysts, absence typically equates to missingness. (53). These types of ‘missing data’ might more accurately be considered as nonrecorded data (54).

Another type of missingness derives from instances where a record may or may not contain multiple versions of a condition. For example, administrative data may record more than one diagnosis associated with a given encounter. Obviously, all patients should have at least one diagnosis associated with an encounter. But not all will have two or three. The second and third data fields for patients who do not have two or three diagnoses will be empty. These data are not 'missing', and are not 'nonrecorded'. They are truly nonexistent. If the recording rule is that 'blank means nonexistent' there is no significant ambiguity in the meaning of the absence for the clinical purposes of the record user.

Given the nature of routine clinical practice, younger and healthier patients are also at higher likelihood of data about them being nonrecorded than those with more

severe and complicated health conditions, as they may visit their family physicians less often and even when they do pay a visit, the physicians may see it as clinically uninformative to record every item of information (55, 56).

Missing data deriving from patient death or loss to follow-up

Very old patients are likely to move into long-term care facilities or to be cared for in hospitals or other specialized settings. This makes the oldest old and the more severe and complicated cases, including those with risk factors and dementia, more likely to be lost to the records than 'healthier' younger people. Linkage of CPCSSN data and long-term care/hospital/death data are encouraged to more precisely identify health outcomes as it has been shown to improve data quality and reduce bias (53). There are a number of ongoing studies using CPCSSN data linked to administrative data, though it was not employed in my study for financial reasons and time limitations.

Potential solutions to reduce the influence of nonrecorded data in the CPCSSN dataset

Regardless of what causes data to be absent from clinical records, researchers who make secondary use the data and are unable to supplement it through direct data collection need to attempt to minimize the resulting selection and other biases to provide estimations which are as accurate and precise as possible. As discussed above, missingness or absence in CPCSSN data may be distinguished into three types: (1) a null value for not being extractable by CPCSSN coders, which could be minimized by improving CPCSSN data processing to pick up more information, especially from free-text fields; (2) a null value indicating non-existence of a condition, which could be fixed using the typical assumption of null value meaning absent condition (53) in which, for example, no indication of dementia would be taken as indicative of a patient being free of it; and (3) a null value due to a lack of data recording for an extant condition. The last one is problematic because it causes misclassification if the 'type 2' assumption is applied.

In terms of data quality improvement, it is helpful to be able to differentiate between the latter two issues. Taking the issue of BMI data as an example of incompleteness in the CPCSSN dataset, and thinking about how best to accommodate it in future analyses, I suggest some solutions to improve the influence of missing and unrecorded data in analyses.

1. Imputation is one of the most common and effective strategies to reduce a proportion of missing data (55, 57). It is appropriate to impute null CPCSSN values for missing at random (58). For variables missing not at random, imputation may lead to underestimation. For example, it is suspected that BMI has a skewed distribution in CPCSSN with a bigger proportion of overweightness and obesity among its patients in comparison to the general population. A possible explanation for this is that people with measurements are more likely to have a problem with their weight, as in being underweight, overweight or obese (48). Evidence also shows that people with a specific chronic health condition, like diabetes mellitus or cardiovascular diseases, are at higher likelihood of having BMI data than those without any disease (48, 59) which may produce a sub-cohort of 'less healthy' patients. In this case, we still could impute but might want to carefully identify a sub-cohort of patients who are highly likely to have BMI recorded, for example, data from a site with close to perfect frequency of BMI measurement, as a training dataset for imputation (60, 61), to choose different categories to impute under different assumptions, for example, imputing only under and normal weight for patients without BMI data under the assumption that people with BMI ≥ 30 are more likely to be recorded (62), or to transform BMI values to obtain a normal distribution (63). These assumptions are difficult to test empirically, and uncertainty about findings from imputation methods remains (58).

   Imputation may also produce errors when applied to variables with a large missing proportion (for example, missing more than 40% (58)).

For the cohort used in my analysis, as the proportion of missing data was 32%, imputation to improve data on BMI may be possible. In order to identify which imputation method is most suitable it is necessary to perform a series of sensitivity analyses which include different amounts (percentages) of cases with missing data using different methods (54). However, as the missingness proportion is fairly high, multiple imputation using linear regression may be the best choice as it includes associations between all variables in the model. Results from multiple imputation are normally overestimated because of the uncertainty of the data and should be used for illustrating data characteristics only (54). Imputing missing or absent BMI values as a continuous variable first, then converting them into categories, may be more appropriate than imputing BMI as categories from the outset. On one hand, it may be that grouping BMIs of 25 to 29.9 is appropriate because they denote the same broad category ("overweight"), differentiating between BMIs of 29.9 and 30 is less appropriate, which would make imputing actual BMI values more accurate. Yet BMI is not linear and categorizing it may make interpretation less complicated and focused on answering the question about the association between being overweight/obese and incident dementia. Approaching the problem empirically by performing both methods and comparing results may be preferable.

2. Another typical solution for missing data is defining a sample to include only participants with all required variables for the intended analysis (complete cases) (55). I used this strategy to include people with age, sex, and 3-digit postal code information (Forward Sortation Area) because the proportion of participants missing age, sex, and FSA is less than 5% and believed to be missing at random, which makes excluding them acceptable and complete-case analysis is more appropriate (54).

   To my knowledge, since there is no evidence for missing BMI data being associated with incident dementia, censoring incomplete cases may be

acceptable depending on the purpose of the analysis (63). I used this method in a sub-analysis to study the association between BMI and dementia onset because it was fairly simple and direct. However, excluding those without BMI data, for example, may skewed the sample characteristics to the right, as discussed in the previous paragraph, introducing selection bias towards a more health problematic cohort, and reducing the study's representativeness and external validity. This might make the findings less appropriate to be applied to a true community-dwelling population. A sensitivity analysis to compare the results of a multiple imputation-developed sample and the restricted, managed-eligibility sample with complete-case analysis which I actually used, may have improved study validity (63). The representativeness in relation to the general community-dwelling population of samples developed for either approach could be established empirically using a selected set of key demographic variables.

3. In support of the methods described above it is important to be as confident as possible about the certainty of the absent value assumption, for example, that people without a BMI record are people without a weight problem. Employing a validation approach for being underweight, overweight, or obese would help our understanding. A possible way to do this is to randomly select representative samples of patients from CPCSSN who do or do not have either a recent BMI recorded in CPCSSN, or height and weight values, to reidentify them, contact them and directly measure their weight and height. Independently, their BMI values recorded in CPCSSN would be noted and used to classify patients as underweight, normal, overweight or obese using the assumption that no indication means absence of the condition: people with no recorded value would be classified as being of normal weight. Comparison between the recorded values with the measured values would indicate whether it is appropriate for the absent value assumption to be applied in identifying people as being underweight, normal weight, overweight, or obese. If it is, using these classifications to populate reference sets for the three conditions,

a machine learning approach could be taken to permutate all available CPCSSN variables (except BMI) to most accurately and precisely impute BMI caseness with optimal validation metrics (53).

In addition, it may be that apparently missing data have been, in fact, recorded in areas of EMRs that CPCSSN does not access, like the notes. CPCSSN data managers may want to investigate this matter in greater detail.

Conclusion

Drawing a picture of risk and protective factors for dementia is a complicated process as it includes many fields, from genetic, educational, social environmental to physical and mental health. Considering the strengths, limitations and lessons learnt while conducting this doctoral thesis, I would suggest that future studies should undertake the following:

1. Development and validation of case definitions through machine learning approaches using EMR data would be hugely beneficial. EMR data are large, rich and reliable data resources which allows such 'Big Data' research to be conducted in a timely and financially efficient way.
2. Create and validate computer algorithms to categorise smoking status more precisely. In this project, I accepted that if a patient has a record of being a smoker in his or her chart, he or she is identified as a smoker despite the lack of time information relating to smoking data. It is clear that the amount and duration of smoking hugely affect its impact on health, and therefore a person who smokes occasionally should not be categorised in the same group as one who smokes a lot over a long period of time.
3. Consider developing extraction and standardization algorithms for risk factor information like alcohol consumption, physical activity or family history, which is recorded non-systematically in primary care data. This would be beneficial not only for dementia-related studies but also research on other chronic diseases.

4. Undertake a similar analysis for blood pressure, as hypotension may cause cerebral under perfusion which later progresses to dementia. This may be implicated in the nonsignificant association between high blood pressure and dementia found in this study.
5. Identify annual weight loss in mid- and late life to examine whether older adults lose weight before a dementia diagnosis and whether this may be an early sign of risk for cognitive impairment.
6. Study blood glucose level, blood lipid level and their medication to see how and how well hypertension in people with dementia is managed in primary care. This would identify an ideal range of blood pressure for best cognitive performance and reserve.
7. Develop a risk score for the incidence of dementia using data recorded in primary care.

In general, this thesis suggested several findings relating to the improvement of dementia diagnosis and management in primary care, as well as the improvement of primary care data quality:

1. Routinely collected health data derived from primary care electronic medical records and processed into a standardized format is a powerful tool to support health research.
2. The incidence of dementia diagnosed in primary care has increased over the period of 2009-2017. Age is strongly related to the increase among community-dwelling patients.
3. Depression and diabetes mellitus, though diagnosed and managed in primary care still has negative impact on dementia, while obesity, dyslipidemia and hypertension do not.
4. Routine screening for cognitive decline on older adults with diabetes mellitus, depression and gradual weight loss might support earlier diagnosis and provision of care and help for those in need.

Further analysis using blood pressure levels instead of dichotomized hypertensive status, blood glucose and/or HbA1C levels instead of dichotomized diabetic status and using blood cholesterol levels instead of dichotomized abnormal blood lipid status might help to resolve questions about the extent to which these laboratory measurements are associated with incidence of dementia. These are intended as part of the next phase of my research programme. The availability of longitudinal data of greater duration from CPCSSN will also allow future research to study a longer period of follow-up.

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APPENDIX

Appendix 1a. Summary of studies of hypertension and dementia

Study	Population (Study)	Sample (N)	Number of cases	Age range (mean ± SD)	Length of follow-up (years)	Predictors	Outcomes	Confounders	Estimates
Kivipelto et al (2001)(46)	Finland	1,409	48	(50.4 ± 6)	21 ± 4.9	SBP, DBP	AD	Age, BMI, education, MI, smoking status, alcohol consumption	OR = 2.8 [1.1-7.2] for SBP ≥ 160
Launer et al (2010) (47)	USA (HHSA)	7,878	491	50+ (56.5)	~25	HTN (SBP ≥ 140)	Dementia	Age, education, smoking, BMI, DM, CHD, CVA	RR = 0.76 [0.65-0.93] for treated RR = 1.05 [0.86-1.27] for untreated
Morris et al (2001) (48)	USA (EPESE)	642	99	65+	13	SBP, DBP	AD	Age, sex, education, interval to disease diagnosis	OR = 1.13 [0.24-5.37] for SBP ≥ 160 OR = 1.56 [0.46-5.32] for DBP ≥ 90
Ninomiya et al (2011) (49)	Japan	668	232	65-79 (72±4)	15 (mid-life) + 17 (late life)	Mid-life and late life BP	All-D, VaD, AD	Age, sex, education, HTN drugs, DM, CKD, total-cholesterol, BMI, stroke, smoking, alcohol	For late life: HR = 0.84[0.54-1.29] for pre-HTN HR. =1.08[069-1.68] for stage1 HTN HR = 1.12 [0.68-1.87] for stage 2 HTN For mid-life: HR = 0.92 [0.60-1.40] for pre-HTN

									HR = 1.51 [1.00-2.29] for stage 1 HR = 1.79 [1.11-2.90] for stage 2
Verghese et al (2003) (50)	USA (Bronx Aging Study)	306	122	75-85	21 (6.7)	SBP, DBP	All-D, AD, VaD	Age, sex, education, HTN, DM, stroke, smoking, HTN drugs	HR = 0.55[0.32-0.96] for AD, stage 2 SBP HR = 1.64 [1.04-2.61] for All-D low DBP HR = 1.91 [1.05-3.48] for AD, low DBP
Whitmer (2005) (51)	USA	8,845	721	40-44	30+	Mid-life HTN	All-D	Age, sex, education, race, TC, DM, smoking	HR = 1.24 [1.04-1.48]
Bermejo-Pareja et al (2010) (52)	Spain (NEDICES)	3,824	159	65+ (72.7 ± 6.2)	3.2 [0.05-6.6]	Treated/ untreated-HTN	Dementia, AD, non-AD	Age, sex, geographical area, educational level, HL, DM, stroke, heart disease, depression, sleep duration	RR = 2.37 [1.32-4.27] for untreated-HTN RR = 1.28 [0.87-1.90] for treated HTN
Fujishima et al (2002) (53)	Japan (Hisayama)	614	103	65+	7	SBP	VaD	Age, SBP, stroke, alcohol, PA, Hasegawa's dementia scale, sex, DM	HR = 1.61 [1.19-2.19]
Kivipelto et al (2005)	Finland	1,883	117	(50.6±6.0)	21±4.9	SBP	All-D	Age, sex, education, follow-up time, BMI, DBP, TC, smoking	OR = 1.97[103-3.77] for SBP ≥ 140
Luchsinger et al (2005) (54)	USA	1,138	246	65+ (76.2±5.9)	5.5±3.2	HTN	AD (pp)	Age, sex, race, education, APOEε4,	HR = 1.5 [0.9-2.4]

								DM, heart disease, smoke	
Ogunniyi et al (2011) (55)	Nigeria	1,733	120	70+	6	HTN, SBP, DBP	All-D	Age, sex, education, smoking, stroke	OR = 1.52 [1.01-2.30] for HTN OR = 1.09 [1.03-1.16] for 10-mmHg SBP OR = 1.22 [1.07-1.38] for 10 mmHg DBP OR = 2.36 [1.20-4.62] for SBP ≥ 160 OR = 1.65 [1.01-2.69] for DBP ≥ 90
Posner et al (2002) (56)	USA	1,259	157 AD, 56 VaD	65+	7	HTN, SBP, DBP	AD, VaD	Age, education, race, heart disease,	RR = 0.8 [0.6-1.1] for AD RR = 1.6 [0.9-2.9] for VaD RR = 0.8 [0.5-1.3] for stage2 SBP RR = 0.9 [0.5-1.5] for stage3 SBP RR = 0.4 [0.1-1.4] for stage2 DBP RR = 2.5 [1.3-4.7] for stage3 DBP
Qiu et al (2010) (57)	Sweden (Kungsholmen)	1,270	428	75+ (81.5±5.0)	5.1 (?-10.5)	SBP, DBP, PP, DM, stroke, HF	All-D, AD	Age, sex, education, APOEε4, survival status, MMSE score, BMI, CHD, HTN drugs, DM	HR = 1.47 [1.02-2.12] for stage1 SBP HR = 1.84 [1.06-3.18] for stage2 SBP
Raffaitin et al (2009) (58)	France (3-City)	7,077	208	65+ (73.4±4.9)	4+	Blood pressure	All-D, AD, VaD	Metabolic syndrome, WC,	HR = 1.06 [0.65-1.70]

								TGs, glycemia, HDL-C	
Reitz et al (2010) (59)	USA	1,051	92	65+ (75.66±6.32)	4.0 ± 1.36	HTN	AD (pp)	Age, sex, DM, smoking, HDL-C, WHR, education, race, APOEε4	HR = 1.158 [0.64-2.11]
Salinas et al (2016) (60)	Mexico (10/66 Dementia Research Group)	1,193		73.2±5.9	3	HTN	All-D	Sex, age, education, study area, depression, MCI, DM, dyslipidemia, obesity, heart disease, stroke, smoking	RR = 0.9[0.7-1.3]
Wang et al (2012) (61)	Taiwan	733,394	8,488	60.0±12.8	9	Matched DM cohort (1:1), HTN	AD	Age, sex, insurance premium, geographic area, urbanization status, cerebrovascular disease, CVD, hyperlipidemia	HR = 1.38[1.30-1.48]
Yoshitake et al (1995) (62)	Japan (Hisayama Study)	828	103	65+	7	SBP	VaD, AD	Age, sex, DM, stroke, alcohol, PA, Hasegawa's dementia scale, hematocrit	HR = 1.61[1.19-2.19]

Appendix 1b. Summary of studies of diabetes and dementia

Study	Population (Study)	Sample (N)	Number of cases	Age range (mean ± SD)	Length of follow-up (years)	Predictors	Outcomes	Confounders	Estimates
Beeri et al (2004) (63)	Israel	1,892 men	309	40-65	35	DM	All-D	Age, area of birth, SES, BMI, TC, HDL-C, SBP, DBP, smoking	OR = 2.87[0.66-12.45] for treated DM OR = 2.89[1.28-6.53] for untreated DM
Whitmer (2005) (51)	USA	8,845	721	40-44	30+	Mid-life DM	All-D	Age, sex, education, race, HTN, TC, smoking	HR = 1.46 [1.19-1.79]
Cheng et al (2012) (64)	Taiwan	40,887		45-85	7	Matched DM cohort	All-D	Age, sex, HTN, AF, dyslipidemia, mood disorder, use of antithrombotic	HR = 1.47[1.16-1.85] for age ≤ 65 HR = 2.30[1.51-3.51] for age > 65
Huang et al (2014)(65)	Taiwan	142,744		58.7±14.0	5.5±3.1	Matched DM cohort	All-D	Age, sex, geographic area, rurality, HTN, hyperlipidemia, stroke, CAD, arrhythmia, HF, depression	HR = 1.76[1.50-2.07]
Haroon et al (2015) (66)	Canada	893,115	169,114	69-78	7.2	Matched DM cohort	All-D	CAD, CVD, PVD, HTN, CKD, SES	HR = 1.16[1.15-1.18]
Kuo et al (2015) (67)	Taiwan	100,775		40+	11	Matched DM cohort	All-D	HTN, hyperlipidemia, CAD, stroke, CKD	HR = 1.26[1.19-1.33] for all age but RR gets smaller over time

Mayeda et al (2013) (68)	USA (Sacramento Area Longitudinal Study on Aging)	1,617	159	60-98	Up to 10 years	DM	All-D	Age, sex, education, WC, stroke	HR = 1.88[1.15-3.07] for untreated DM HR = 2.38[1.65-3.34] for treated DM
Neergard et al (2016) (69)	Denmark	5,512 women	592	70+	15 (11.9±3.9)	DM	All-D, AD, VaD	Age, education, smoking, alcohol, PA, SBP, BMI, TC, depression, other vascular and neural disorders	HR = 1.25[1.05-1.49] for all-D HR = 1.33[1.02-1.74] for AD HR = 1.23[0.63-2.36] for VaD
Peila et al (2002) (70)	USA (HHP)	2,574		70-91	3	DM	All-D, AD, VaD, AD without CVD	Age, education, APOEe4, midlife SBP, TC, BMI, ABI, stroke	RR = 1.4[0.8-2.4] for incident DM RR = 1.6[0.97-2.5] for prevalent DM
Salinas et al (2016) (60)	Mexico (10/66 Dementia Research Group)	1,193		73.2±5.9	3	DM	All-D	Sex, age, education, study area, depression, MCI, HTN, dyslipidemia, obesity, heart disease, stroke, smoking	RR = 2.4[1.4-2.9]
Wang et al (2012) (61)	Taiwan	733,394	8,488	60.0±12.8	9	Matched DM cohort (1:1)	AD	Age, sex, insurance premium, geographic area, urbanization status, cerebrovascular disease, CVD, HTN, hyperlipidemia	HR = 1.45[1.38-1.52]
Yoshitake et al (1995) (62)	Japan (Hisayama Study)	828	103	65+	7	DM	VaD, AD	Age, sex, SBP, stroke, alcohol, PA,	HR = 2.09[0.91-4.81]

								Hasegawa's dementia scale, hematocrit	
Xu et al (2004) (71)	Sweden (Kungsholmen)	1,301	350	75+	4.7 (0.01-8.3)	DM	All-D, VaD, AD	Age, sex, education, heart disease, stroke, SBO, DBP, HTN drugs, BMI	HR = 1.5[1.0-2.1]
Xu et al (2007) (72)	Sweden (Kungsholmen)	1,173	397	75+	9	Incidence borderline DM	All-D, VaD, AD	Age, sex, education, MMSE, follow-up survival status, BMI, heart disease, stroke, SB, DBP, HTN drugs	HR = 1.61 [1.19-2.19] for all-D HR = 1.98[1.12-3.50] for AD
Xu et al (2009) (73)	Sweden (Kungsholmen)	1,248	420	75+	9	Borderline DM, DM	All-D, VaD, AD	Age, sex, education, MMSE, APOE, follow-up survival status, BMI, heart disease, stroke, SB, DBP, HTN drugs	HR = 1.77[1.10-2.84] for borderline DM HR = 3.37[1.48-7.68] undiagnosed DM
Xu et al (2009) (74)	Sweden (HARMONY)	13,693	467	65+		Mid and late life DM	All-D, VaD, AD	Age, sex, education, stroke, heart disease, HTN, BMI	OR = 1.89[1.51-2.38] OR = 2.76[1.97-3.87] for mid-life DM OR = 1.63[1.23-2.16] for late life DM
Fujishima et al (2002) (53)	Japan (Hisayama)	614	103	65+		DM	VaD	Age, SBP, stroke, alcohol, PA, Hasegawa's dementia scale, sex, HTN	HR = 1.61 [1.19-2.19]

Luchsinger et al (2005) (54)	USA	1,138	246	65+ (76.2±5.9)	5.5±3.2	DM	AD (pp)	Age, sex, race, education, APOEε4, HTN, heart disease, smoking	HR = 3.8 [1.8-4.2]
Qiu et al (2003) (75)	Sweden (Kungsholmen)	1,270	428	75+ (81.5±5.0)	5.1 (?-10.5)	DM	All-D, AD	Age, sex, education, APOEε4, survival status, MMSE score, BMI, CHD, HTN drugs, HTN	HR = 1.50 [1.08-2.10] for all-D HR = 1.52 [1.03-2.25] for AD
Reitz et al (2010) (59)	USA	1,051	92	65+ (75.66±6.32)	4.0 ± 1.36	DM	AD (pp)	Age, sex, HTN, smoking, HDL-C, WHR, education, race, APOEε4	HR = 1.586 [0.83-3.01]
Raffaitin et al (2009) (58)	France (3-City)	7,077	208	65+ (73.4±4.9)	4+	DM	All-D, AD, VaD	Metabolic syndrome, WC, TGs, glycemia, HDL-C, blood pressure	HR = 1.58 [1.05-2.38]

Appendix 1c. Summary of studies of dyslipidemia and dementia

Study	Population (Study)	Sample (N)	Number of cases	Age range (mean ± SD)	Length of follow-up (years)	Predictors	Outcomes	Confounders	Estimates
Kivipelto et al (2005) (76)	Finland	1,883	117	(50.6±6.0)	21±4.9	TC	All-D	Age, sex, education, follow-up time, SBP, DBP, BMI, smoking	OR = 1.89 [1.02-3.49] for TC > 251 mg/dL
Mielke et al (2005) (77)	Sweden	382	93	70	18	TC, TGs	All-D	Sex, education, smoking, BMI, DBP, stratified by 5-year age range	TC 70: HR = 0.62 [0.46-0.83] for 75-79 TC 75: HR = 0.71 [0.51-1.00] for 75-79 TC 70: HR = 0.77 [0.61-0.96] for 79-88 TC 75: HR = 0.70 [0.52-0.93] for 79-88 TC 80: HR = 0.73 [0.55-0.98] for 79-88
Whitmer (2005) (78)	USA	8,845	721	40-44	30+	Mid-life high TC	All-D	Age, sex, education, race, HTN, DM, smoking	HR = 1.42 [1.22-1.66]
Li et al (2005) (79)	USA (Adult Changes in Thought)	2,141	273	65+	5.6 (±1.8)	TC, HDL	All-D, AD	Age, sex, education, CASI score, BMI, HTN, CAD, CVD, DM	Not significant
Salinas et al (2016) (60)	Mexico (10/66 Dementia Research Group)	1,193		73.2±5.9	3	dyslipidemia	All-D	Sex, age, education, study area, depression, MCI, HTN, DM, obesity, heart disease, stroke, smoking	RR = 1.0[0.6-1.5]
Reitz et al (2010) (59)	USA	1,051	92	65+ (75.66±6.32)	4.0 ± 1.36	Low HDL-C	AD (pp)	Age, sex, HTN, smoking, DM, WHR, education, race, APOEε4	HR = 1.6 [0.77-3.32]

Raffaitin et al (2009) (80)	France (3-City)	7,077	208	65+ (73.4±4.9)	4+	Low HDL-C	All-D, AD, VaD	Metabolic syndrome, WC, TGs, glycemia, blood pressure, DM	HR = 1.05 [0.68-1.62]
Tan et al (2003) (81)	USA (Framingham)	1,026	77	(76.1±5.3)	9	TC, HDL	AD	Age, sex, APOEε4, CHD, lower lipid agents, BMI	HR = 0.97 [0.90-1.05] for TC HR = 1.10 [0.93-1.31] for HDL HR = 1.01[0.92-1.11] for TC15-20

Appendix 1d. Summary of studies of obesity and dementia

Study	Population (Study)	Sample (N)	Number of cases	Age range (mean ± SD)	Length of follow-up (years)	Predictors	Outcomes	Covariates	Estimates
Beydoun et al (2008) (82)	USA (Baltimore Longitudinal Study of Aging)	2,322	187	50+	23.4 [0.01-66.01]	BMI, WC	AD	Age, sex, race, education, smoking, year of birth, HTN, DM, CVD, dyslipidemia	HR = 6.05 [2.14-17.09] for underweight at age 30 HR = 11.89 [2.82-50.05] for underweight at age 40 HR = 11.21[2.65-47.30] for underweight at age 45
Gustafson et al (2009) (83)	Sweden (Prospective Population Study of Women)	(last exam) 660 women	110	38-60	32	BMI, WHC	All-D	Age, education, alcohol, TGs, TC	HR = 0.91 [0.65-1.27] for BMI ≥ 25 at age 38-60 OR = 0.50 [0.26-0.96] for BMI ≥ 25 at age 62-84 OR = 0.26 [0.12-0.59] for BMI ≥ 25 at age 70-92
Hassing et al (2009) (84)	Sweden	1,152	312	(52.5±4.6)	40	BMI	All-D, AD, VaD	Age, sex, education, smoking, alcohol, HTN, CHF, MI, DM, stroke	OR = 1.55 [1.18-2.04] for all-D OR = 1.68 [1.21-2.33] for AD

									OR = 1.36 [0.82-2.56] for VaD
Kivipelto et al (2005) (76)	Finland (CAIDE)	1,883	117	(50.6±6.0)	21±4.9	BMI	All-D	Age, sex, education, follow-up time, SBP, DBP, TC, smoking	OR = 2.10 [0.97-4.55] for BMI > 30
Qizilbash et al (2015) (85)	UK (CPRD)	1,958,191	45,507	40+	15 (9.1[6.3-12.6])	Underweight, overweight, obese	All-D	Age, sex, smoking, alcohol, DM, MI, statin use, HTN drugs	RR = 1.34 [1.30-1.39] for underweight RR = .81 [0.79-0.83] for overweight RR = 0.74 [0.72-0.76] for obese I RR = 0.69 [0.66-0.74] for obese II RR = 0.67 [0.60-0.74] for obese III
Salinas et al (2016)(60)	Mexico (10/66 Dementia Research Group)	1,193		73.2±5.9	3	Central obesity	All-D	Sex, age, education, study area, depression, MCI, HTN, dyslipidemia, DM, heart disease, stroke, smoking	RR = 0.9[0.6-1.3]
Whitmer et al (2005) (78)	USA	10,276	713	40-45	30+	Underweight, overweight, obese	All-D	Age, race, marital status, sex, HTN, DM, TC	HR = 1.24 [0.70-2.21] for underweight HR = 1.35 [1.14-1.60] for overweight HR = 1.74 [1.34-2.26] for obese

Fitzpatrick et al (2009) (86)	USA (Cardiovascular Health Study)	2,798	480	40+ 65+ (74.7)	(5.4)	Mid- and late life BMI and obesity	All-D, AD, VaD	Age, sex, race, education, C-reactive protein level, interleukin 6 level, HTN, DM, CHD, TC, ankle-arm index, smoking, activities, APOEε4	Mid-life: HR = 1.01[0.98-1.04] Late life: HR = 0.95 [0.92-0.98]
Tolppanen et al (2014) (87)	Finland (CAIDE)	1,304	99	50.2 ± 6.0		Mid- and late life BMI and obesity	All-D, AD	Age, sex, APOEε4, FSA, smoking, education, income, DM, CVD, SBP, TC	HR = 1.07 [1.00-1.4] for mid-life BMI HR = 0.94 [0.86-1.03] for lte life BMI HR = 1.14 [1.03-1.25] for decease in BMI HR = 1.81 [0.91-3.57] for mid-life obesity HR = 0.55 [0.23-1.34] for late life obesity
Atti et al (2008) (88)	Sweden (Kungsholmen)	646		75+	9	BMI	All-D	Age, sex, education, baseline MMSE, depression, chronic disease, impairment in daily activities	HR = 0.75 [0.59-0.96] for BMI ≥ 25HR = 0.97 [0.71-1.34] for BMI < 20
Dahl et al (2008) (89)	Finland	605	86	70.8 ± 5.5	8	BMI	All-D	Age, sex, education, CHD, HTN, AF, stroke, DM, smoking, alcohol	HR = 0.92 [0.87-0.97]

Hughes et al (2009) (90)	USA (Kame)	1,478	129	65+ (71.8)	7.8±0.3	BMI, BMI change	All-D, AD, VaD	Age, race, education, alcohol, smoking, HTN, DM, angina pectoris, stroke, TIA, PA APOEε4	HR = 0.80 [0.38-1.68] for baseline BMI HR = 0.31[0.09-1.02] for BMI change
Luchsinger et al (2012) (91)	USA	1,459	145	65+ (75.9 ± 6.5)		BMI, WC, WHR quartiles	Alzheimer's disease	Age, sex, race, education, APOEε4, DM, HTN, heart disease, non-HDL-C, HDL-C, stroke	HR = 0.4[0.2-0.7] for 2nd quartile HR = 0.7[0.4-1.2] for 3rd quartile HR = 0.6[0.3-1.1] for 4th quartile
Neergaard et al (2016) (92)	Denmark	5,512 women	592	70+	15 (11.9±3.9)	BMI	All-D, AD, VaD	Age, education, smoking, alcohol, PA, SBP, DM, TC, depression, other vascular and neural disorders	HR = 0.88 [0.45-1.72] for BMI < 18.5 HR = 0.75 [0.62-0.89] for BMI [25-30] HR = 0.79[0.62-1.01] for BMI ≥ 30
Nourhashémi et al (2003) (93)	France (PAQUID)	3,557		77.6±6.4	1-8	BMI	All-D	Age, sex, age-sex interaction, education, alcohol, smoking	RR = 1.19 [0.72-1.96] for BMI < 21 RR = 0.72[0.43-1.20] for BMI ≥ 27

Acronyms in tables

HTN: Hypertension
DM: Diabetes mellitus
DL: Dyslipidemia
HL: Hyperlipidemia
AD: Alzheimer's disease
VaD: vascular dementia
Mixed-D: mixed-dementia
All-D: dementia of all types
HHP: Honolulu Heart Program
HAAS: Honolulu Asia Aging Study
CHD: coronary heart disease
CVA: cerebrovascular accident
pp: probable and possible dementia
CKD: chronic kidney disease
BMI: Body-mass index
SBP: Systolic blood pressure
DBP: Diastolic blood pressure
PP: Pulse pressure
CASI score: Cognitive Abilities Screening Instrument score