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Determinants of Time to Diagnosis in Young-Onset Dementia

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Abstract

Timely diagnosis of young-onset dementia (YOD) is critical. This study aimed to identify factors that increased time to diagnosis at each stage of the diagnostic pathway. Participants were patients diagnosed with YOD (n = 40) and their care partners (n = 39). Information was obtained from questionnaires, and review of medical records. Mean time from symptom onset to YOD diagnosis was 3.6 ± 2 years. Suspicion of depression/anxiety at presentation was associated with significantly increased time from presentation to specialist referral. Neurologist-diagnosed YOD was the fastest route to a diagnosis, whereas diagnoses made by other specialists significantly increased the time from first specialist visit to diagnosis. By investigating multiple stages of the diagnostic pathway, we identified two factors that increased time to diagnosis: suspicion of depression/anxiety at presentation delayed specialist referral from primary care, and diagnosis by a specialist other than a neurologist delayed diagnosis of YOD.

Keywords

young-onset, dementia, diagnosis, delay, determinants

Introduction

Young-onset dementia (YOD) is defined as dementia with symptom onset before the age of 65,[1] and is also known as early-onset dementia. YOD is caused by a number of distinct conditions that have a diversity of presenting symptoms, including those in cognitive, behavioural, psychiatric, and neurological domains.[2] Most prevalence studies report that Alzheimer's disease is the most common cause of YOD, followed by vascular dementia and frontotemporal dementia (FTD).[3] These three causes account for 50%–75% of all cases in most studies,[4] although it is likely that dementia with Lewy bodies also makes a significant contribution.[5] A recent meta-analysis determined that the global prevalence of YOD is 119 per 100000 population aged 30-64.[3] We have reported similar prevalence in New Zealand: approximately 140 per 100 000 population aged 30-64.[6] Subsequently, studies from the UK,[7] Finland[8] and Italy[9] have reported similar prevalence estimates; Yi et al have reported considerably higher global YOD prevalence estimates: over 300 per 100 000 population.[10]

People living with YOD and their loved ones experience different challenges and have different needs to those with dementia onset after 65.[11-16] The specific needs of people

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Data Availability Statement included at the end of the article

living with YOD are increasingly being recognised, and clinicians are urged to improve care for this patient group.[17]

YOD takes longer to diagnose than late onset dementia. Previous studies have compared time to diagnosis from symptom onset, defined as the date of the earliest signs or symptoms noticed by the patient or a knowledgeable informant. One study reported an average of 4.4 years from symptom onset to YOD diagnosis, compared to 2.8 years for late onset dementia.[16] Another has reported an even wider gap: 4.4 years for YOD vs 1.3 years for late onset dementia.[18] Most recently, Chiari et al[19] reported an average of 41.8 months from symptom onset to YOD diagnosis, which was significantly longer than late onset dementia (30.6 months). Medical records indicated that the mean time from symptom onset to diagnosis was 3.2 years[20] and 3.4 years[21] in two separate Australian studies.

Delayed diagnosis is a major burden on patients, families, and caregivers.[16] People with YOD and their care partners frequently express concern about the stressful delays and uncertainty they experience when obtaining a diagnosis.[12,14,22,23] FTD care partners identified getting an early and accurate diagnosis as one of the greatest challenges they faced.[24,25] Even in the absence of disease-modifying treatments, timely diagnosis of YOD is critical. The benefits of a timely diagnosis include: best-practice management of the condition, including symptomatic treatment; awareness of the prognosis; access to support services; access to genetic counselling for at-risk family members if the dementia is familial; and the opportunity to adjust to the consequences of the disease and plan for the future.[16] Additionally, the emergence of approved disease modifying therapies for the most common cause of YOD – Alzheimer's disease – further emphasises the importance of early, accurate diagnosis.[26,27] Previous research in this area has highlighted the importance of timely diagnosis, and identified a need for studies focused on the causes of delayed diagnosis.[16]

To date, six studies have directly assessed the effect of one or more factors on the time to diagnosis of YOD: three in Australia,[12,20,21] one in Norway and Sweden,[28] one in the Netherlands,[16] and one in Italy.[19] These studies identified a number of factors that were associated with increased time to diagnosis, including younger age at onset,[12,19-21] presentation with depression,[19,20] presentation with FTD,[16,20,28] presentation with dementia other than Alzheimer's disease or behavioural variant FTD,[21] and increased number of services consulted.[21] Strikingly, attending a specialized YOD service decreased time to diagnosis by approximately 12 months.[21]

Previous studies have generally investigated time to diagnosis for a single period: time from symptom onset to dementia diagnosis.[12,16,21,28] Chiari et al.[19] and Draper et al.[20] also investigated time from symptom onset to first assessment. The aim of the current study was to identify factors that influence time to diagnosis at multiple stages of the diagnostic pathway, including primary and specialist presentation. We utilised both self-report data and medical records to comprehensively investigate all factors that have been studied in the literature, providing the most nuanced description of YOD diagnosis to date.

Methods

Participants

Participants were patients who had been diagnosed with YOD in New Zealand, and their care partners. Patients without care partners or whose care partners did not wish to participate were included. Care partners of deceased patients who had been diagnosed with YOD in New Zealand were eligible to participate. A convenience sample was obtained through referrals from clinicians, or self-referral in response to advertising via social media and community support groups. All patients were consented in person, or via video call if a face-to-face meeting was not possible. If the patient was deceased, their care partner provided written consent.

The inclusion criteria were:

1) The patient must have been diagnosed with YOD, defined as meeting the clinical diagnostic criteria for dementia and having symptom onset before age 65. Symptom onset was defined as the date of the earliest sign/s or symptom/s noticed by the patient or the care partner, whichever was earlier, as recorded in medical records. This definition was chosen to align with previous studies.[12,16,19-21,29] On the basis of available medical records, the patient must have met the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, criteria for 'major neurocognitive disorder,' or internationally accepted criteria for a dementia sub-type diagnosis (eg, behavioural variant FTD). Clinical dementia diagnoses were independently verified by consensus review of medical records by two expert clinicians (a neuropsychologist (C.I.) and a neurologist (K.B.)) who had not been involved in the patient's clinical care. Verification of dementia diagnosis did not involve assessment of the patient. If the two expert clinicians could not reach a consensus, they sought the opinion of a third expert clinician who had not been involved in patient care (C.L.H. or K.W.). If a consensus could not be reached the participant was excluded. If C.I. and/or K.B. had been involved in the patient's clinical care, clinical dementia diagnosis was independently verified by additional expert clinicians (C. L. H. and/or K.W.). Diagnosis of the underlying condition that causes dementia (ie, dementia sub-type) was not necessary for inclusion. Dementia diagnoses were not confirmed by neuropathology in any case; however, diagnoses were confirmed with highly sensitive biomarkers (PET/CSF) or genetic testing in some cases (n = 10).

2) If the patient had diminished capacity to consent, they were deemed capable of giving consent to participate using supported decision making.
3) The care partner must have been caring for or have cared for a patient with a diagnosis of YOD, as defined in (1).

Exclusion criteria were:

1) Inability to screen for patient consent because in-person screening was impractical due to location, and screening via video calling was insufficient to determine ability to consent.
2) Inability to screen for YOD diagnosis due to unavailability of medical records.
3) Lack of consensus by expert clinicians to independently verify dementia diagnosis.
4) Clinical diagnosis of YOD was not made in New Zealand.
5) Clinical diagnosis of YOD was made prior to January 1, 2015.

Data Collection

With informed consent (from the patient or, if the patient was deceased, from the care partner), the patient's medical records were obtained from primary care and/or hospital records. Information about dementia diagnosis, presenting symptoms, investigations, referrals, and clinical history were extracted. Two researchers independently reviewed medical records to minimize inaccuracies (B.R. and S.S.).

Participants (both patients and care partners) were asked to complete questionnaires that included multiple-choice questions about participant demographics and the patient's medical history, family history of dementia, presenting symptoms, and diagnosis. Care partners were encouraged to support the patients to complete the questionnaire if necessary. Discrepancies between medical records and questionnaire information were resolved in different ways: dates and diagnoses recorded in medical records took precedence over dates and diagnoses reported by participants, but other discrepancies were resolved by verification with participants and clinicians, where possible.

Data Analysis

Descriptive statistics were used to summarise participants' demographic and clinical characteristics, and features of the diagnostic pathway.

Inferential statistics were used to determine factors that affected time to diagnosis. Time to diagnosis was assessed in three phases:

1. Time from first clinical presentation to dementia diagnosis
2. Time from first presentation to a general practitioner (GP) to first specialist consultation
3. Time from first specialist consultation to dementia diagnosis

Inferential statistics were not used to determine factors that affected time to diagnosis from symptom onset, as the specific date of symptom onset could not be determined.

The independent variables were all factors that were potential barriers to diagnosis, including dementia subtype, patient demographics, clinicians in pathway, and investigations (Suppl Table 1). The effect of each potential barrier on time to diagnosis (in each of the phases) was assessed using Cox proportional hazards modelling. Proportional hazards assumption was checked using Schoenfeld residuals. For each phase, all independent variables that were associated with time to diagnosis according to univariable Cox regression were included in multiple regression Cox proportional hazard modelling. Independent variables that increased the Akaike Information Criterium (AIC) value were omitted from multiple regression models. Individuals were excluded from these analyses if there were missing data. Statistical significance (Wald test) was set at $P > 0.05$. All statistical analyses were performed with R software, version 4.3.2 (2023-10-31 ucrt).

Results

Forty patients with a diagnosis of YOD were included in this study. Of these patients, 39 had a care partner who also took part in the study. The recruitment process and reasons for exclusion are summarised in Figure 1.

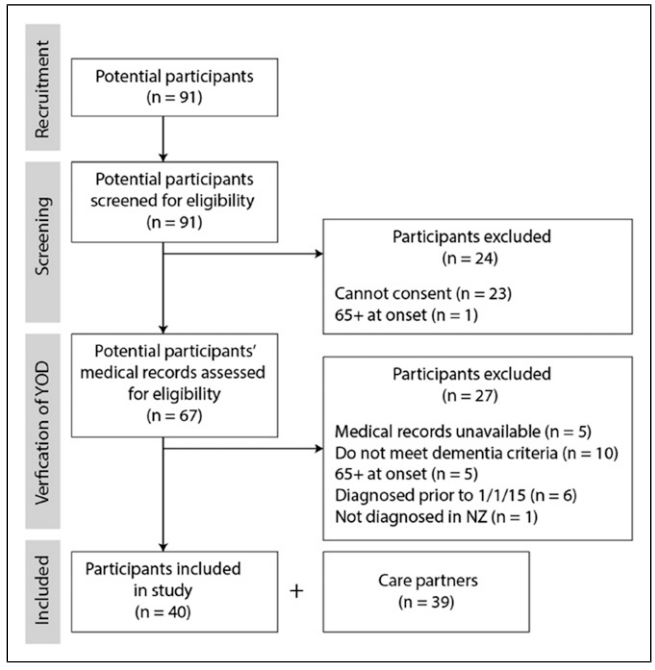

Figure 1. Participant flow diagram indicating the number of potential participants, reasons for exclusion, and screening process.

Demographic Characteristics of Participants

Demographic characteristics of patients and care partners are summarised in Table 1. Sixty-two percent of patients were male. Our recent prevalence study identified a slight majority (56%) of males with diagnosed YOD,[6] but the over-representation of male patients in the current study may reflect selection bias. The majority of patients and care partners had a post-high school qualification (65% and 56%, respectively) and most had English as their first language (98%; 97%). Most patients (93%) were working at symptom onset. The majority of patients (93%) and care-partners (92%) were of NZ European ethnicity, reflecting selection bias: the New Zealand population is approximately 70% NZ European and we have reported an increased YOD prevalence in non-European ethnicities ie, Māori and Pacific People.[6] Unfortunately, this selection bias precluded sub-group analyses by ethnicity. Most care partners (92%) were in a relationship with the patient (married/civil union/de facto).

Features of Diagnostic Pathway

Diagnostic pathway features are summarised in Table 2. The mean age of symptom onset was 55 (range 42-63; s.d. 4.6). On average, the delay between symptom onset and first clinical presentation was 16 months (range: 0-59; s.d. 16.5). In five cases there was no apparent delay between symptom onset and first clinical presentation. When care partners (or patients without care partners) were asked about patient reluctance to present to a health professional, 12/38 (32%) reported that patients "were reluctant to first visit the doctor". All but three patients (92%) presented to a general practitioner (GP) at their first presentation. Most patients knew the health professional they presented to "quite well" or "very well" (30/35; 85%).

All patients that presented to a GP were referred to a specialist for diagnosis, in line with New Zealand guidelines.[30] Mean time from GP presentation to specialist referral was 10 months (range 0-73; s.d. 17.5). In 55% of cases (16/29), GPs referred to a specialist within 3 months, but specialist referral took over 12 months in 24% of cases (7/29). The mean delay between GP referral to a specialist and the first specialist visit was 1.9 months (range 0-5; s.d. 1.5); 81% of patients were seen by a specialist within 3 months of referral.

Once a patient had been assessed by a specialist, the mean time to diagnosis was 16.4 months (range: 0-75; s.d. 17.5). Five patients were given a YOD diagnosis at the first specialist visit. All patients were ultimately diagnosed with YOD by a specialist: 75% by a neurologist, 15% by a psychiatrist, 5% by a geriatrician, and 5% by a neuropsychologist. Of these, 9/40 (23%) were diagnosed in a specialist YOD clinic.

The mean number of clinicians in the pathway to YOD diagnosis was 3.4 ± 1.4 (range: 2-8). All but one patient presented to a GP at some point during the diagnostic process (97%). Most patients (85%) were referred to a neurologist at some point during the pathway to YOD diagnosis. Seventeen patients (46%) were classified as having MCI before they were diagnosed with dementia.

Mean age at diagnosis was 59 (range: 48-71; s.d. 5.2). Mean time from symptom onset to dementia diagnosis was 43.5 months (range: 5-101; s.d. 24.1; 3.6 ± 2 years). Mean time from first clinical presentation to dementia diagnosis was 27.2 months (range: 2-89; s.d. 22.1). Dementia sub-type was not yet determined for 3 patients. In one case, the dementia sub-type (CADASIL) was diagnosed before the diagnosis of YOD, because dementia was not a presenting symptom of CADASIL. Of the remaining 36 patients, 28 (78%) were given a sub-type diagnosis at the same time as the YOD diagnosis; the longest time between YOD diagnosis and sub-type diagnosis was 9 months.

Table 1. Demographic Characteristics of Participants.

	Patient n = 40	Care-partner n = 39
Female	15 (38%)	27 (69%)
Male	25 (62%)	12 (31%)
Ethnicity[a]		
NZ European	37 (92.5%)	36 (92.3%)
Māori	1 (2.5%)	1 (2.6%)
Other	2 (5%)	2 (5.1%)
Highest qualification[b]		
High school	13 (32.5%)	11 (28.2%)
Post-high school	25 (65%)	22 (56.4%)
English as first language	39 (97.5%)	38 (97.4%)
Marital status at diagnosis		
Married/civil union/de facto	37 (92.5%)	-
Widowed	1 (2.5%)	-
Single	2 (5%)	-
Location at diagnosis		
Rural	7 (17.5%)	-
Urban	33 (82.5%)	-
Children[c]	29 (73%)	-
Lived alone at onset	2 (5%)	-
Employed at onset	37 (93%)	-
Relationship to patient		
Married/civil union/de facto	-	36 (92.3%)
Parent	-	1 (2.6%)
Child	-	1 (2.6%)
Housemate	-	1 (2.6%)

All data are presented as counts and percentage, or mean ± standard deviation.
[a]Prioritised ethnicity.
[b]No data for 2 patients and 9 care partners.
[c]No data for 6 patients.

Clinical Characteristics

Clinical history prior to first dementia presentation was determined from medical records and via self-report (Table 3). According to medical records, a history of mental illness (23%), concussion/traumatic brain injury/head injury (29%) and smoking (28%) were relatively common. History of alcohol or substance abuse was rare (5%) and a history of exposure to toxic chemicals was not reported for any patients.

Table 2. Features of Diagnostic Pathway (n = 40).

Age at onset (y)[a]	55.4 ± 4.6
Age at first presentation (y)[a]	56.6 ± 5.1
Time from onset to first presentation (m)[a]	16.0 ± 16.5
Was patient reluctant before first visit?[b]	
Yes	12 (32%)
No	26 (68%)
First health professional consulted[c]	
General practitioner	34 (92%)
Neuropsychologist	1 (3%)
Hospital admission	2 (5%)
How well did first health professional know patient?[d]	
Very well	18 (51%)
Quite well	12 (34%)
Not at all	5 (14%)
Age at first referral to specialist[e]	57.5 ± 5.3
Time from first presentation (if GP) to first referral to specialist (m)[f]	10.2 ± 17.5
Time from GP referral to specialist to first specialist visit (m)[f]	1.9 ± 1.5
Age at first specialist visit[e]	57.5 ± 5.3
Time from first specialist visit to dementia diagnosis (m)[e]	16.4 ± 17.5
Age at general dementia diagnosis (y)	59.4 ± 5.2
Time from onset to diagnosis of dementia (m)[a]	43.5 ± 24.1
Time from first visit to diagnosis of dementia (m)[a]	27.2 ± 22.1
Diagnosing doctor (YOD)	
Neurologist	30 (75%)
Psychiatrist	6 (15%)
Geriatrician	2 (5%)
Neuropsychologist	2 (5%)
Diagnosed by specialist YOD clinic	9 (23%)
Number of clinicians in pathway to YOD diagnosis	3.4 ± 1.4
Clinicians consulted in pathway to YOD diagnosis	
General practitioner[a]	38 (97%)
Neurologist	34 (85%)
Neuropsychologist	15 (38%)
Psychiatrist	14 (35%)
Geriatrician	5 (13%)
ED/general medicine/specialist physician	4 (10%)
Ophthalmologist	3 (8%)
Respiratory physician	2 (5%)
Haematologist	1 (3%)
Sub-type diagnosis	
Age at sub-type diagnosis (y)[h]	58.9 ± 5.0[k]
Time from YOD diagnosis to sub-type diagnosis (m)[i]	0.8 ± 1.9
Time from onset to sub-type diagnosis (m)[i]	42.0 ± 22.5[k]
Classified as having MCI[j]	
Yes	17 (46%)
No	20 (54%)

Data are presented as counts and percentages or mean ± standard deviation. ED: Emergency department; GP: General practitioner; MCI: mild cognitive impairment; YOD: young-onset dementia.
[a]Not reported for 1 participant.
[b]Not reported for 2 participants.
[c]Not reported for 3 participants.
[d]Not reported for 5 participants.
[e]Not reported for 4 participants.
[f]Not reported for 2 participants; specialist referral not made by GP for 3 participants.
[g]Not reported for 4 participants; specialist referral not made by GP for 3 participants.
[h]Sub-type not yet determined for 3 participants.
[i]Not applicable for 1 participant; sub-type not yet determined for 3 participants.
[j]Not reported for 3 participants in medical records
[k]This is less than age at/time to general dementia diagnosis because the patient with CADASIL was diagnosed with CADASIL before they were diagnosed with dementia.

Table 3. Clinical Characteristics of Patients (n = 40).

	Medical Records	Self-Report
Clinical history prior to dementia onset		
Mental illness	9 (23%)	3 (9%)[a]
Alcohol/substance abuse	2 (5%)	2 (6%)[a]
Concussion/TBI/head injury	11 (29%)[b]	13 (37%)[a]
Smoking	11 (28%)	9 (25%)[c]
Exposure to toxic chemicals[d]	0	11 (31%)[a]
First symptoms[e]		
Memory difficulties	30 (79%)	-
Change in personality	12 (32%)	-
Difficulty paying attention	8 (21%)	-
Impaired language	8 (21%)	-
Apathy/social withdrawal/lack of interest	3 (8%)	-
Change in behaviour	3 (8%)	-
Headache	2 (5%)	-
Movement	1 (3%)	-
Stroke	1 (3%)	-
Was the patient aware of the first symptoms?[b]		
Yes	-	20 (53%)
No	-	18 (47%)
Dementia sub-type[f]		
AD/PCA/logopenic AD	23 (57.5%)	14 (42.5%)
Frontotemporal dementia/PPA	8 (20%)	5 (15.2%)
Dementia with lewy bodies	3 (7.5%)	3 (9.1%)
Parkinson's Disease dementia	1 (2.5%)	1 (3%)
Alcohol-related dementia	1 (2.5%)	0
Vascular dementia/CADASIL	1 (2.5%)	1 (3%)
Not yet determined	3 (7.5%)	5 (15.2%)
Don't know	-	4 (12.1%)
Family history of LOD[a]		
Yes	11 (31%)	-
No	24 (69%)	-
Family history of YOD[b]		
Yes	3 (8%)	-
Possible	3 (8%)	-
No	32 (84%)	-

Data are presented as counts and percentages. AD: Alzheimer's disease; CADASIL: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; LOD: late-onset dementia; PCA: posterior cortical atrophy; PPA: primary progressive aphasia; TBI: traumatic brain injury; YOD: young-onset dementia.
[a]Not reported for 5 participants.
[b]Not reported for 2 participants.
[c]Not reported for 4 participants.
[d]Not reported for any participants in medical records.
[e]All symptoms counted if more than one reported. Defined as symptoms reported at first presentation to GP and/or specialist. Unclear for 2 participants.
[f]Not reported in 7 participant questionnaires.

When patients (or care-partners if the patient was deceased) were asked to indicate whether they had experienced these conditions, mental illness was under-reported (9%) and exposure to toxic chemicals was reported by 11/35 patients (31%).

Presenting symptoms were determined from medical records (Table 3). The most common presenting symptoms were memory difficulties (79%), change in personality (32%), difficulty paying attention (21%), and impaired language (21%). When care partners were asked about patient awareness of the first symptoms, 20/38 (53%) reported that patients were aware of symptoms before the first presentation.

Dementia sub-type was extracted from medical records (final recorded sub-type) and via self-report (Table 3). According to medical records, the most common sub-type was Alzheimer's disease, including posterior cortical atrophy (PCA) and logopenic Alzheimer's disease (57.5%), followed by FTD, including behavioural variant and primary progressive aphasia (20%). When patients were asked whether they had been given a sub-type diagnosis, 5 (15%) reported that the sub-type was not yet determined and a further 4 (12%) did not know.

According to medical records, one third of patients (11/35; 31%) reported a family history of late-onset dementia (first-degree relative) and 3/38 (8%) reported a confirmed family history of YOD. In a further 3 patients there was a possible history of YOD.

Investigations during the diagnostic pathway were extracted from medical records (Table 4). The majority of patients underwent MRI (35/40; 88%) and/or CT (22/40; 55%). PET and SPECT imaging were less common. One patient (3%) did not undergo any neuroimaging during the diagnostic pathway, and 3 patients (8%) underwent CT only. Lumbar puncture for CSF analysis was undertaken in 7 cases (18%), and was requested but unsuccessful in a further 2 cases. Genetic testing was offered to 6 patients (16%) and accepted by 5 (13%).

Table 4. Investigations During Diagnostic Pathway (n = 40).

Neuroimaging	
MRI	35 (88%)
CT	22 (55%)
PET (FDG or amyloid)	6 (15%)
SPECT	2 (5%)
None	1 (3%)
CT only	3 (8%)
Lumbar puncture[a]	
Yes	7 (18%)
No	31 (78%)
Requested but unsuccessful	2 (5%)
Genetic testing	
Yes	5 (13%)
No	34 (85%)
Offered and declined	1 (3%)

Data are presented as counts and percentages. CT: computed tomography; FDG: fluorodeoxyglucose; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: Single-photon emission computed tomography.
[a]Lumbar puncture for analysis of cerebrospinal fluid amyloid beta and tau.

Over one third of participants reported that the patient's GP had been "dismissive or unhelpful" during the diagnostic process (13/37; 35%; Table 5). Twenty-seven percent (10/37) reported that a health professional other than the patient's GP was "dismissive or unhelpful". In total, almost half of the participants (18/37; 49%) reported that either the patient's GP or another health professional was "dismissive or unhelpful".

Determinants of Time to Diagnosis

We first investigated the effect of variables of interest on time from first presentation to dementia diagnosis. Twenty-eight variables were included in univariable Cox regression analyses (Suppl Table 1). Of these, only one variable had an effect: suspicion of depression/anxiety at presentation increased time to diagnosis (hazard ratio (HR) = 0.48, 95% CI: 0.24-0.96; Table 6). Next, we split the time to diagnosis into two phases: 1) time from first presentation to a GP to first specialist visit, and 2) time from first specialist visit to dementia diagnosis. Only participants who presented to their GP initially and were referred to a specialist by their GP (n = 29) were included in the former analysis. These analyses indicated that suspicion of depression/anxiety significantly increased the time from first GP presentation to first specialist visit (hazard ratio (HR) = 0.26, 95% confidence interval (CI): 0.08-0.81, $P = 0.02$, Table 6), but did not have an effect on time from first specialist visit to dementia diagnosis. These data suggest that suspicion of depression/anxiety upon GP presentation is associated with delayed referral to a specialist.

Univariable analyses indicated that one other variable was significantly associated with time from first GP presentation to first specialist visit: patient awareness of symptoms. This significantly decreased the time from first GP presentation to first specialist visit (HR = 3.01, 95% CI: 1.26-7.21, $P = 0.01$). However, multiple regression analyses including both suspicion of depression/anxiety and patient awareness of symptoms indicated that the effect of patient awareness of symptoms was not significant in this model (Table 6). Therefore, the only variable that had a significant effect on

Table 5. Care Partner/Patient Perceptions of Clinicians (n = 37).

GP was dismissive/unhelpful	
Yes	13 (35%)
No	24 (65%)
Other health professional was dismissive/unhelpful	
Yes	10 (27%)
No	27 (73%)
Either GP or other health professional was dismissive/unhelpful	
Yes	18 (49%)
No	19 (51%)

Data are presented as counts and percentages. Data are self-reported by care partners. If care partner report was unavailable, data are self-reported by patients. GP: general practitioner.

Table 6. Cox Proportional Hazards Modelling Results at Each Stage of the Diagnostic Pathway.

Diagnostic Stage	N	Variable	Median in months (Range)	*P*	HR	95% CI	
Presentation to dementia diagnosis	37	Depression/anxiety at presentation					
		Yes	40 (3-75)	**0.04**	0.48	0.24	0.96
		No	13.5 (2-89)	-	-	-	-
Presentation to specialist visit[a]	26	Depression/anxiety at presentation					
		Yes	19 (0-54)	**0.02**	0.26	0.08	0.81
		No	3.5 (0-16)	-	-	-	-
		Awareness of symptoms					
		Yes	2.5 (0-22)	0.26	1.73	0.66	4.6
		No	12 (3-54)	-	-	-	-
Specialist visit to dementia diagnosis	37	Diagnosing doctor					
		Neurologist	11 (0-32)	-	-	-	-
		Other	28 (0-75)	**0.01**	0.27	0.10	0.73

In bold, *P* values indicating significant variables ($p < 0.05$).
[a]Multiple regression results.

time from first presentation to GP, to first specialist visit was suspicion of depression/anxiety.

Finally, we determined whether any variables of interest were associated with time from first specialist visit to dementia diagnosis (n = 37). Univariable analyses indicated that the diagnosing doctor and history of smoking had an effect, so these two variables were included in multiple regression analysis. Multiple regression analyses indicated that the effect of history of smoking was not significant in this model and it increased the variability in the model so it was removed from multiple regression analyses. The only variable that had a significant effect on time from first specialist presentation to diagnosis was diagnosing doctor: being diagnosed by a doctor other than a neurologist was associated with increased time (HR = 0.27, 95% CI: 0.10-0.73, $P = 0.01$; Table 6).

Discussion

This research has identified factors that delay YOD diagnosis at multiple timepoints in the diagnostic pathway, adding to the existing literature and providing further information to facilitate timelier diagnosis. The key findings from this study are that suspicion of depression/anxiety at presentation delayed referral from primary to specialist care, and that diagnosis by a neurologist decreased time from first specialist visit to YOD diagnosis. The total time from symptom onset to YOD diagnosis was 3.6 years, which is remarkably similar to the total time reported in two recent studies: 3.5 years in an Italian cohort[19] and 3.4 years in an Australian cohort.[21]

The first potential hurdle in the diagnostic pathway is delayed presentation for clinical assessment. In the current study, patients did not present to a clinician until 16 months after symptom onset on average. This is a shorter delay than that reported in an Australian cohort: Draper et al.[20] reported that symptoms of YOD were present for a median of 2.3 years before first clinical contact. The reasons for delayed presentation in our cohort are unclear. A precise date of symptom onset could not be determined, precluding statistical analysis of factors that may delay presentation. In our cohort one third of care partners (32%) reported that patients were reluctant to present clinically before their first visit; however, we could not determine whether this reluctance was associated with increased time from symptom onset to presentation. It is also important to acknowledge that this 16-month 'delay' could in fact represent a period when clinical presentation is not necessary or helpful; for example, symptoms may take this long to develop or persist before a clear picture emerges.

Following clinical presentation, time to diagnosis was 27.2 months on average. We investigated various demographic and clinical factors that may have delayed this stage of the diagnostic process. We found that suspicion of depression/anxiety at presentation was associated with delayed diagnosis, in keeping with previous studies that have shown an association between depression and time to diagnosis.[19,20] By investigating multiple periods of the diagnostic pathway, we have clearly demonstrated that this is driven by delayed referral from primary to specialist care, rather than increased time to diagnosis following specialist referral. Presentation with neuropsychiatric symptoms is more likely in YOD than late onset dementia and it is well known that distinguishing YOD from a primary psychiatric illness can be challenging.[31] Worsening symptoms over time can be used to distinguish neurodegenerative from primary psychiatric causes, but this can take months. Recommended strategies to differentiate primary psychiatric illness from YOD include analysis of biomarkers, involvement of a neurologist and a psychiatrist, and tests of social cognition.[32] Increased awareness among primary care clinicians that YOD can be difficult to distinguish from primary psychiatric illness may mitigate this delay in specialist referral.

Specialist referral is recommended for all suspected cases of YOD,[30] so we investigated how frequently this occurred in our cohort. The majority of patients (92%) first presented to a GP and all of these patients were subsequently referred to a specialist for diagnosis. The mean time from first GP presentation to specialist referral was 10 months; in 55% of cases, GPs referred to a specialist within 3 months. However, specialist referral took more than 12 months in 24% of cases, indicating that delayed specialist referral lengthens time to diagnosis in some cases. Time from referral to specialist consultation did not seem to contribute to delayed diagnosis: 81% of patients were seen by a specialist within 3 months of referral and the maximum time from referral to specialist consultation was 5 months. These results suggest that the majority of GPs are appropriately referring suspected YOD cases to specialists in a timely manner. However, in a minority of cases, GPs are delaying referral to specialists which may be increasing time to diagnosis. Similarly, Chiari et al[19] demonstrated that diagnosis of YOD takes longer than late onset dementia diagnosis because of a longer delay between symptom onset and specialist presentation (rather than longer diagnostic workup), suggesting a need for increased awareness of YOD in primary care, and in the general population.

Following specialist consultation, time to diagnosis was 16.4 months on average. If the diagnosis was made by a neurologist, this phase of diagnosis was shorter. This result suggests that referral to a neurologist may be the most appropriate course of action for suspected YOD. It is also possible that patients presenting to non-neurologists were more likely to have atypical or complex presentations, leading to increased time to diagnosis, and/or that neurologists had better access to diagnostic tools, for example molecular biomarkers. In contrast to Loi et al.[21]'s finding in an Australian cohort, we did not find that attending a specialized YOD clinic decreased time to diagnosis. However, we acknowledge that small sample size may have caused our study to be underpowered to detect this effect.

This study has a number of strengths. Firstly, YOD diagnoses were determined from medical records and independently validated by a neurologist and a neuropsychologist with YOD expertise, giving us confidence that all included patients had been accurately diagnosed. Secondly, we gathered data from both self-reported questionnaires (patient and care partner) and from all available medical records, allowing us to comprehensively investigate the diagnostic pathway from symptom onset to YOD diagnosis. Thirdly, we considered numerous demographic and clinical factors that may affect time to diagnosis, including all factors that have been reported in previous literature.

This study was limited by a relatively small sample size, which may have precluded detection of small or moderate effects in statistical analyses. This may explain why we did not identify an effect of factors that have been reported to affect time to diagnosis in previous studies, for example dementia sub-type, age at symptom onset, and presentation to a specialized YOD clinic. Small sample size also limited our ability to analyse sub-groups by dementia sub-type. This study was also limited by its reliance on a convenience sample of patients and care partners, potentially leading to selection bias. Unfortunately, the ethnicity of participants in this study was not representative of ethnic diversity in the New Zealand population, as most participants were NZ European. It was therefore not possible to analyse sub-groups by ethnicity. This is an important limitation, as there is evidence that Māori, Pacific, and Asian ethnicities access dementia support differently to NZ Europeans and that prevalence of YOD is higher in Māori and Pacific People.[6] Further research on YOD diagnosis in these communities is warranted. Finally, this study was limited by our inability to accurately determine date of symptom onset. This limitation is common to all studies of dementia diagnosis, due to the insidious nature of dementia onset, delayed clinical presentation, and recall bias. We attempted to mitigate this limitation by using the most reliable data sources to determine the date of symptom onset as precisely as possible. Nonetheless, we were unable to determine an exact day or month of symptom onset in any case. Therefore, we focused our statistical analyses on time from first presentation, rather than symptom onset.

In summary, we have determined that the average time from symptom onset to YOD diagnosis was 3.6 years, potentially representing a significant delay for patients and families. We identified two factors that were associated with increased time to diagnosis: suspicion of depression/anxiety at presentation and diagnosis by a specialist other than a neurologist.

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Author Contributions

B. Ryan designed the study, supervised the data collection and wrote the paper. S. Sharma, C. Ilse, K Brickell, C. Le Heron, and K. Woods collected the data and assisted with writing the article. A. O'Mara Baker, L. Tippett and M. A. Curtis assisted with writing the article.

Declaration of Conflicting Interests

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Ethical Statement

Ethical Approval

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethics approval was obtained from the New Zealand Health and Disability Ethics Committee (Reference: 20/STH/130).

Consent to Participate

Informed consent to participate was written. All patients were consented in person, or via video call if a face-to-face meeting was not possible. If the patient was deceased, their care partner provided written consent.

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Data Availability Statement

The datasets generated during the current study are available from the corresponding author on reasonable request.

Supplemental Material

Supplemental material for this article is available online.

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