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Review Article

Epidemiology and Etiology of Young Stroke

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Introduction. Stroke in people under 45 years of age is less frequent than in older populations but has a major impact on the individual and society. In this article we provide an overview of the epidemiology and etiology of young stroke. *Methods*. This paper is based on a review of population-based studies on stroke incidence that have included subgroup analyses for patients under 45 years of age, as well as smaller community-based studies and case-series specifically examining the incidence of stroke in the young. Trends are discussed along with the relative frequencies of various etiologies. *Discussion*. Stroke in the young requires a different approach to investigation and management than stroke in the elderly given differences in the relative frequencies of possible underlying causes. It remains the case, however, that atherosclerosis contributes to a large proportion of stroke in young patients, thus, conventional risk factors must be targeted aggressively.

1. Introduction

Stroke incidence rises steeply with age; therefore, stroke in younger people is less common; however, stroke in a young person can be devastating in terms of productive years lost and impact on a young person's life. As will be outlined below, some causes of stroke are more frequent in adults under 45 years of age compared to more aged populations [1]. We here provide an overview of the incidence and etiology of young stroke.

While a specific definition of "young stroke" is lacking, the vast majority of authors consider "young stroke" to pertain to individuals under 45 years of age. Hence, this paper is based on a review of population-based studies on stroke incidence that have included subgroup analyses for patients under 45 years of age, as well as smaller community-based studies and case-series specifically examining the incidence and etiology of stroke in the young. Individual studies and reviews were found by performing a medline search (1948-present) using the search terms "young stroke," "ischaemic stroke and young," "ischemic stroke and young," "haemorrhagic stroke and young," "hemorrhagic stroke and young," as well as "epidemiology and young stroke" and "etiology and young stroke." We also collected papers by examining the references cited in these articles and selecting those pertaining to the epidemiology of young stroke. Finally, we examined prevalence in large population registries that provided subgroup analyses for patients younger than 45 years of age. These were identified using the search terms "epidemiology and stroke" and "population-based studies and stroke." Again, references were examined to identify other stroke registries, which were examined with regard to prevalence among young patients under age 45.

2. Incidence of Young Stroke

Differences in methods of reporting the incidence of young stroke make it difficult to draw geographical comparisons. While the majority of population-based studies report rates for all stroke combined (ischaemic and haemorrhagic, including subarachnoid haemorrhage), a few report rates for ischaemic stroke alone. Furthermore, referral bias needs to be considered when hospital-based registries as opposed to community-based studies are used to examine the relative proportion of young stroke, as is often the case in developing countries. Moreover, incidence has been examined at different time points over several decades and incidence rates

may change overtime. Finally, where authors have reported incidence rates by age decile, it is apparent that even within the "young stroke" category, incidence increases sharply with age, particularly among the 34 to 44 year old age group [2–12].

Despite these difficulties, some general trends are apparent. Overall incidence rates under the age of 45 range from 7 to 15 in 100 000 people/year for all stroke (ischaemic and haemorrhagic) [13–17], with higher rates reported in some countries [18]. A few studies reporting similar incidence rates have examined all stroke in the 15 to 44 year old age group [19, 20] or ischaemic stroke only in the 15 to 49 year old age group (6.6 to 11.4 in 100 000 people/year) [21–23]. Under the age of 35, rates are less than 10 in 100 000 people/year (ranging from 0 to 9) [3, 4, 9, 24]. Within the 35 to 44 year old age range, rates range from 22 to 45 in 100 000 people/year [2–12]. There may be a greater incidence of stroke in developing countries, such as Libya with a reported rate of 47 in 100 000 people/year for all stroke under the age of 45 [18]. High rates have also been observed in Japanese adults (70 in 100 000 in the 35 to 44 year old age group) [25], Hispanics (26 in 100 000 in the 22 to 44 year old age group) [26], and American blacks with a relative risk of 5 for all stroke reported for blacks compared to whites (96 in 100 000 versus 19 in 100 000) within the 35 to 44 year old age group in the Greater Cincinnati/Northern Kentucky Stroke Study from 1993-1994 (an RR of 2.2 was observed in the 0 to 34 year old age group) [24, 27]. This trend is supported by the results of the Northern Manhattan Stroke Study demonstrating a nonsignificant trend of increased risk among blacks aged 22 to 44 years old [26], as well as the Baltimore Washington Co-op Young Stroke study [28, 29]. Interestingly, two studies of Caribbean blacks demonstrate similar stroke rates to those reported in other young stroke populations [9, 11], suggesting that the increased risk among young blacks in the United States might be related to socioeconomic variables, although high rates are observed in South African blacks of all ages [30, 31]. Very high young stroke rates were also observed in a rural population from Northern Portugal [32].

With regard to sex differences in the incidence of young stroke, rates are greater among men than women in the 35 to 44 year old age group [2, 4, 10, 14]. Some population-based studies demonstrate an increased incidence among women under 30 years old [22, 33, 34], as do several case-series [34–36].

3. Etiology of Young Stroke

While a greater proportion of strokes are due to subarachnoid haemorrhage and intracranial haemorrhage in young adults (40–55%) compared to the general stroke population (15–20%), [17, 26, 37], cerebral infarction is still most common. An increased risk of cerebral infarction among young adults with conventional vascular risk factors is observed, particularly in developing countries due to increasing smoking rates and urbanization [38], as well as among young blacks and Taiwanese patients with more adverse risk factor profiles resulting in a greater relative contribution of small vessel disease to young stroke [39, 40]. However, other causes of stroke in young adults differ in frequency from those observed in the elderly [41]. This holds particularly true in adults under 30 years of age.

In terms of etiology and relative strength of risk factors, most data comes from clinical series and case-control studies. The majority of these have examined adults less than 45 years of age, while the Helsinki Young Stroke registry examined etiology in adults under 49 years of age [21]. In as many as 35% of cases, the underlying etiology remains unclear [21, 23, 29, 33, 34, 36, 42–44]. Importantly, while atherosclerosis remains an important risk factor (accounting for 15–25% of strokes in young adults [36], and an even greater proportion among certain ethnicities) [40, 45], cardioembolic stroke is more common among younger patients (15–35% of cases) [21, 29, 33, 34, 36, 42, 43, 45]. Other causes that are more frequent in young people include extracranial artery dissection (2–25% of cases) [21, 29, 36, 40, 42, 46], migraine (up to 20% of cases [42], although thorough studies excluding alternate possible causes suggest migraine contributes to just 1–5% of cases [23, 29, 33–36]), and drug use (up to 5% of cases, depending on the frequency of use in a given population [29]). Oral contraceptive use has been implicated in up to 8% of cases of young stroke in some populations [43]. Apart from antiphospholipid antibody syndrome (5–10% of cases) [23, 29, 33, 34, 36, 42, 45], inherited coagulation disorders do not appear to play a large role in young stroke in the absence of right to left venoarterial shunting [47]. Sickle cell disease, in which 7 to 10% of affected individuals experience strokes before the age of 20 [48], and rheumatic valvular heart disease are important in some populations, with as many as 32% of cases of young ischaemic stroke attributable to rheumatic heart disease in Iran [49]. Cerebral venous thrombosis is an uncommon cause of young stroke (i.e., <1% of cases [50]), as are rare causes of nonatherosclerotic arteriopathies (although they contribute to 15–35% of cases of young stroke as a collective group [36]). These include Sneddon's syndrome; Moyamoya disease (responsible for 6–15% of cases due to nonatherosclerotic arteriopathy (22–27% of all young ischaemic stroke) in Asian populations [40, 45]); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); vasculitis; prior chemoradiotherapy; HIV infection (up to 7% of cases of young stroke in Nigeria [51]); and neoplasm. While only specifically examined and demonstrated in young patients in South Africa, in addition to sickle cell disease and rheumatic heart disease, a higher prevalence of stroke secondary to vasculitis due to infection likely occurs in developing countries [38].

With regard to stroke in women, oral contraceptive use is associated with a 2- to 5-fold increased risk of stroke of all subtypes, depending on the estrogen content, although there is some controversy as to whether pills with a low estrogen content (i.e., less than 50 micrograms of ethinyl estradiol) are truly associated with an increased risk given the discrepancy in results between cohort studies, which do not support a link, and a large number of case-control studies that do [52]. This risk is increased in smokers and in

those who experience migraine with aura [53]. Less common causes of stroke that are more common in women include systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome (APLAS), central venous thrombosis (CVT), reversible cerebral vasoconstriction syndrome (RCVS), Susac syndrome, Takayasu's arteritis, Moyamoya disease, Sneddon's syndrome, and fibromuscular dysplasia. In addition, women are particularly susceptible to stroke in the puerperium.

4. Cardioembolic Stroke

Different frequencies of the various causes of cardioembolic stroke are reported, and geographical variation is seen. The methods and criteria that are used to identify potential causes also vary. Mitral valve disease, which accounts for a significant proportion of cardioembolic stroke in young patients, is more common in some populations due to a high prevalence of rheumatic heart disease [49]. The relative contribution of rheumatic heart disease (in the presence or absence of synthetic valve prosthesis) and mitral valve prolapse to cardioembolic stroke varies widely among different geographical regions and stroke registries from 40–70% in most studies [33, 36, 40, 43, 49], and far less in the Helsinki registry given the virtual disappearance of rheumatic fever in Finland [21]. The prevalence of dilated cardiomyopathy also demonstrates geographical variation in light of the increased prevalence of Chagas disease in South America (also associated with intramural thrombi) [54], as well as the increased prevalence of alcohol abuse among certain populations. Rates range from 4–17% [21, 36]. Reports identify atrial fibrillation in 2–20% of young patients who have experienced a cardioembolic stroke [21, 33, 37, 38, 40, 47], more commonly in the setting of rheumatic heart disease [49], which is still less than that observed in older populations [43]. Other potential causes of cardioembolic stroke include acute myocardial infarction and subacute bacterial endocarditis. Rarely, aortic valve disease or left ventricular thrombi are implicated. The relationship between presence of a patent foramen ovale and ischaemic stroke is complex.

5. Patent Foramen Ovale (PFO) and Stroke

The potential link between PFO and young stroke remains a controversial subject. Somewhere in the area of twenty-five percent of the population have a PFO, which in itself is not associated with an increased incidence of first ever stroke in large population studies [55], although a nonsignificant trend toward an association has been observed, particularly among individuals under the age of 60 with an atrial septal aneurysm (ASA) [55–57]. PFO is, however, a more common finding among young patients who present with cryptogenic stroke [55]. A meta-analysis of nine case-control studies (566 patients and 459 nonstroke controls), the majority of which examined patients under 55 yo, found that young patients with cryptogenic stroke had an OR of 6.0 for having a PFO compared to young patients with a known cause of stroke (the OR of having a PFO was 3.0 for all young stroke pts) [55, 56]. The concurrent presence of an ASA, found in 2.2% of the population [55], likely adds further risk [55, 57]. Reports examining whether the presence of large septal defects might confer additional risk have yielded contradictory results [55].

6. Thrombophilia in the Setting of PFO and Stroke

With the exception of APLAS, while thrombophilia on its own is probably not associated with ischaemic stroke, there is some evidence to suggest that the prothrombin gene mutation, in particular, might confer a greater risk of ischaemic stroke in the setting of a PFO. As nongenetic laboratory assays in the assessment of coagulopathies may be unreliable in the acute phase of stroke [58], the most reliable studies use genetic testing to identify patients with inherited thrombophilias.

In the largest case-control study examining this issue ($n = 125$; mean age 34.7), an increased incidence of the prothrombin gene mutation in particular (as well as more than one thrombophilic defect) was found among young stroke patients with a PFO compared to those with infarction unrelated to presence of a PFO [47]. The results of three smaller case-control studies are inconsistent [59–61]. The role of FV61691A and TT MTHFR mutations is even less clear with weak or no demonstrated link observed in the absence of more than one defect [47, 59]. Two retrospective reviews of recurrent stroke in patients referred for PFO closure have demonstrated a greater incidence of recurrent stroke among those with thrombophilia; however, the thrombophilic groups have included patients with APLAS (for which there is a known association with stroke) and evidence of thrombophilia on biochemical testing alone, making it difficult to tease out the relative contribution of genetically-determined inherited thrombophilias to the observed increased risk [62, 63].

7. Migraine and Stroke

The weight of evidence from case-control studies suggests that migraine, particularly migraine with aura, is associated with an increased risk of ischaemic stroke in young women under 45 years of age [53, 64–69]. The pathophysiological mechanism underlying this remains unclear. For one, it is difficult to tease out the relative contribution of cases in which migraine precedes ischaemia (i.e., in which stroke occurs secondary to cerebral hypoperfusion during the aura phase), comprising a migrainous infarct, from cases in which migraine with aura is experienced secondary to ischaemia. True migrainous infarcts are probably rare and tend to affect the posterior circulation [53]. It is also possible that young patients with a history of migraine have an increased incidence of stroke due to a shared underlying etiology which predisposes to both. Migraine as a risk factor for future ischaemic stroke seems to apply mostly to young women, and the relative risk may be as high as 3-fold in those who experience migraine with aura [53]. Several associations which might predispose to stroke in migraineurs have been identified in a small number

of case-control studies, including carotid artery dissection [70, 71] and the presence of a patent foramen ovale [72–75]; however, this does not explain the observed sex difference in the frequency of ischaemic stroke among migraineurs [53]. What is known is that there is an additive risk of stroke in women who experience migraine with aura that smoke, with a greater than 3-fold increase in risk, as well as in those who use the oral contraceptive pill, in whom the risk is quadrupled [53]. An OR of 34 to 35 has been reported for young women who smoke, use the oral contraceptive pill, and experience migraine with aura [53].

8. Stroke in the Puerperium

Stroke complicates an estimated 34 in 100 000 deliveries [76], although reported incidence rates vary from 4 to 210 in 100 000 deliveries ($RR = 3$) [77–80], contributing to at least 12% of maternal deaths [81–83]. Some reports suggest that ischaemic and haemorrhagic stroke occur in roughly equal proportions [81, 84, 85], although ischaemic stroke was more common in one study [86]. Treadwell et al. propose that this may be due to differences in patient subgroup selection since some studies exclude stroke secondary to cerebral venous thrombosis, which contributes to a significant proportion of ischaemic strokes in the puerperium (38% in one series [86], although lower and higher rates have been reported [87, 88]). Nonetheless, arterial occlusion remains most common [86, 88]. Most strokes occur peri- or postpartum [86, 89] with a relative risk of 8.7 for ischaemia in the first six weeks postpartum [82, 85], during which cerebral vein thrombosis is also more common [81, 89, 90], and a relative risk of 5.6 for intracerebral haemorrhage during pregnancy [81, 91]. Looking at intracerebral and subarachnoid haemorrhage combined, a 2.5-fold increased risk of haemorrhagic stroke has been reported in pregnancy, and a 23.8-fold increased risk postpartum [81, 91]. Half of cases of aneurysmal rupture in women under the age of 40 occur in pregnancy [81, 92]. Causes of stroke in pregnancy include haemorrhagic and ischaemic stroke in the setting of pre-eclampsia and eclampsia (25–45% of patients with pregnancy-related stroke) [81, 85, 91], arterial dissection, peripartum cardiomyopathy, paradoxical embolism, amniotic fluid embolism, postpartum cerebral angiopathy, and cerebral vein thrombosis. Cerebral haemorrhage is the most common cause of death in patients with eclampsia but associations between pre-eclampsia and eclampsia and ischaemic stroke are also observed [76, 85, 93]. Subarachnoid haemorrhage is the third leading cause of nonobstetric-related maternal death [77, 81], often secondary to aneurysmal rupture [85, 91]. Whether or not the presence of a patent foramen ovale alone is associated with an increased stroke risk in pregnancy has not been properly examined, nor has the incidence of pregnancy-related stroke in association with peripartum cardiomyopathy. Post-partum angiopathy, a reversible cerebral vasoconstriction syndrome usually occurring in the first week postpartum, may be more common than initially thought, although the exact incidence is unknown. It may or may not be associated with pre-eclampsia or eclampsia and cases have also been seen in association with vasospastic drugs, such as ergonovine and bromocriptine during pregnancy [78, 79, 81].

9. Antiphospholipid Antibody Syndrome

Ischaemic stroke was the most common presentation of arterial thrombosis in 1000 patients (mean age 42 ± 14 years) fulfilling the Sapporo criteria [80, 94] for antiphospholipid syndrome (stroke was the incident event in 13% of patients and TIA in 7%) in a large cohort study [95]. There is little doubt that such patients are at increased risk. However, although case-control studies have uniformly demonstrated a higher prevalence of antiphospholipid antibodies among young people who have experienced ischaemic stroke [96–100], studies documenting the persistence of antiphospholipid antibodies following ischaemic stroke in the young are lacking. Ischaemia may transiently induce antiphospholipid antibodies, and prospective studies examining the stroke incidence among patients found to have antiphospholipid antibodies in the absence of an incident event have not been performed [101]. Whether or not the presence of lupus anticoagulant poses a greater risk than other antiphospholipid antibodies remains unclear. Consistent associations between young ischaemic stroke and the presence of lupus anticoagulant and anticardiolipin antibodies are seen [96–100, 102, 103], although there are conflicting reports regarding the significance of anticardiolipin antibodies in older stroke populations [104–106]. Interpretation is complicated by methodological differences and the use of different cut-off values with stronger associations observed at higher titre cutoffs.

With regard to the increased incidence of young stroke among patients with systemic lupus erythematous found to have antiphospholipid antibodies, lupus alone is associated with an increased incidence of cerebrovascular events, which can be mediated by targeting conventional risk factors. As such, it is difficult to tease out the relative contribution of antiphospholipid antibodies in these patients.

10. Nonatherosclerotic Vasculopathies

Cervical artery dissection, migraine, vasculitis, including primary cerebral angiitis, infection (including HIV), radiation vasculopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), reversible cerebral vasoconstriction syndrome (RCVS), Moyamoya, Sneddon's syndrome, Fabry's disease, and malignancy, all come under the heading of nonatherosclerotic arteriopathies. The most common of these in young stroke patients is cervical artery dissection (CAD), which has been implicated in up to 20–25% of cases of young stroke [21, 23, 42], followed by vasculitis related to infection (up to 7% of cases depending on the geographical region [51]), Moyamoya in Asian populations (6–15% of cases of nonatherosclerotic vasculopathy [40, 45]), and migraine (probably closest to 1–5% of cases [21, 23, 29, 33–36]). While, as

a collective group, the remaining nonatherosclerotic vasculopathies contribute to 7–25% of cases of young stroke along with CAD, migraine, infection, and Moyamoya [36, 40, 43, 45], each is responsible for less than 1% of cases. Many of the nonatherosclerotic vasculopathies demonstrate ethnic, geographical, and genetic links making them more common in some populations than others. Similar to Moyamoya, Takayasu's arteritis is more common in Asian females for example (approximately 1% of cases of nonatherosclerotic arteriopathy in Korea) [45]. Vasculitis related to infection as a cause of young stroke is more common in developing countries and in geographical regions with a high prevalence of HIV [51]. Primary cerebral angiitis, a rare cause of stroke, is more common in middle-aged men [107], and MELAS is a maternally inherited mitochondrial disorder. Reversible cerebral vasoconstriction syndrome, which may be underrecognized, is more common in females [108], as is Sneddon's syndrome [109], while both familial and sporadic cases of CADASIL have been described [110, 111].

It should be noted that, apart from primary cerebral angiitis, systemic vasculitides rarely involve the intracranial vessels to produce stroke. Rather, concurrent atherosclerotic disease (and rarely nonbacterial thrombotic endocarditis) is a much more important cause of stroke in patients with systemic lupus erythematosus, for example.

11. Extracranial Arterial Dissection

Cervical artery dissection (CAD) accounts for up to one fifth of ischaemic strokes in young and middle-aged patients [23, 112, 113]. In a majority of cases, the specific etiology remains unknown. Trauma, infection, migraine, fibromuscular dysplasia, and a range other causes have been linked with CAD but evidence to support strong links is limited [112, 114].

With regard to CAD epidemiological observations suggest that some as-yet unrecognized predisposing factors could be heritable [112, 115–117]. A recent meta-analysis has observed a probable link with Ehlers-Danlos but no other consistent associations, although there is little doubt that genetic factors play a role given the high proportion of connective tissue defects noted on specimens and the observed clustering of CAD in families [112]. Environmental triggers, such as infection, are likely also important [112].

12. Haemorrhagic Stroke

The largest studies indicate that subarachnoid and intracranial haemorrhage comprise 25–55% of all strokes under the age of 45 [17, 26, 118, 119] with reported incidence rates ranging from 3 to 6 in 100 000 people/year for subarachnoid haemorrhage, and 2 to 7 in 1 000 000 people/year for intracranial haemorrhage under the age of 45 [18, 20, 26, 120] (the greatest reported incidence rates are for adults aged 20 to 44 in the Northern Manhattan Stroke Study, while other studies have examined adults from age 15 to 44).

The known association between hypertension and intracranial haemorrhage may explain the increased rate of intracranial haemorrhage observed among young blacks in America [26, 39], with one study specifically demonstrating an increased incidence of hypertensive intracranial haemorrhage among young blacks [39]. A relatively high proportion of intracranial haemorrhage has also been noted in young Nigerians, although the analysis was hindered by the inability of many patients to afford a CT scan [51]. An increased risk of intracerebral haemorrhage has also been observed in Hispanics in the Northern Manhattan Stroke Study [26]. This issue has not been well examined among young Asians, apart from a study in North India that did not find an increased proportion of haemorrhagic to total strokes (i.e., only 14% of cases were haemorrhagic) [121] compared to Western countries (with reported proportions in the range of 40–55% of all young strokes [17, 26, 119]). A relatively low proportion of haemorrhagic stroke has also been observed in Saudia Arabia (13% of cases) [122]. Larger scale population studies are required to explore this further. Vascular malformations (aneurysms and arteriovenous malformations) were found in 49% of patients in a retrospective evaluation of 200 cases of intracranial haemorrhage in a tertiary medical centre in Mexico [123]. A high proportion of haemorrhagic stroke secondary to vascular malformations has also been reported in developing countries, although formal angiography is less accessible and reported frequencies are somewhat lower [121].

An important consideration in young persons presenting with intracerebral haemorrhage is the possibility of illicit drug use. In a large American population-based study examining drug use among young patients hospitalized with haemorrhagic ($n = 937$) or ischaemic ($n = 998$) stroke, increased young haemorrhagic stroke rates were observed in association with increased rates of amphetamine and cocaine abuse over a period of three years. An odds ratio of 5 (95% CI 3.24–7.55) for young haemorrhagic stroke in the setting of amphetamine abuse, and 2.33 (95% CI 1.74–3.11) in the setting of cocaine abuse was observed. Cocaine abuse was also associated with an increased rate of ischaemic stroke (OR 2.03; 95% CI 1.48–2.79) [124]. There is now a convincing body of evidence to suggest a high prevalence of underlying cerebrovascular abnormalities among patients experiencing ICH or SAH in association with cocaine and other drug abuse [125].

13. Conclusion

In summary, stroke in the young requires a different approach to investigation and management than stroke in the elderly given differences in the relative frequencies of possible underlying causes. Haemorrhagic stroke is common, and vascular imaging is recommended given a high frequency of underlying vascular anomalies. It is also important to explore the possibility of illicit drug use in these cases. With regard to ischaemic stroke, the increased frequency of dissection mandates a high index of suspicion for imaging the extracranial and intracranial vessels. Whilst the commonest cause of cardioembolic stroke in the elderly is atrial fibrillation, in a young patient transoesophageal echocardiography looking for the presence of a patent foramen ovale ± an atrial septal

aneurysm will have a higher yield. One must not forget, however, that atherosclerosis still contributes to a large proportion of stroke in young patients and likely explains at least some of the ethnic differences noted in the incidence of stroke, emphasizing the need for aggressive risk factor management. This, as well as differences in the prevalence of other causative etiologies, such as rheumatic fever and infection, combined with a younger background population age distribution, may contribute to an increased incidence of young stroke in developing countries. Finally, the incidence of stroke appears greater in women than men under the age of 30, and women are at increased risk of haemorrhage and infarction in the puerperium. Additional history, including use of the oral contraceptive pill, and testing for antiphospholipid antibodies is important in young women.

There is a need for further research in young stroke, particularly population-based studies utilising standardised methodology. These will provide clarity by enabling comparison of incidence rates between countries and trends overtime, and insights into underlying etiological mechanisms.

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