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ORIGINAL ARTICLE

Community-Sourced Reporting of Mortalities in Angelman Syndrome (1979–2022)

Adriana T. Gomes[1] | Amanda Moore[2] | Meagan Cross[3] | Cristy Hardesty[4] | Kelly David[5] | Maria Galan Sampedro[6] | Sophie Dube[7] | Sharon Weil-Chalker[8] | Adela Gentil Montepagano[9] | Ursula Christel[10] | Rachel Martin[11] | Anne Wheeler[12] | Wen-Hann Tan[13] | Lynne M. Bird[14] | Terry Jo Bichell[15]

[1]UCSD, San Diego, California, USA | [2]Angelman Syndrome Foundation, Aurora, Illinois, USA | [3]FAST Australia, Salisbury, Australia | [4]Patient Advocate, New Market, Alabama, USA | [5]Foundation for Angelman Syndrome Therapeutics (FAST), Austin, Texas, USA | [6]FAST Spain, Almería, Almería, Spain | [7]Angelman Quebec Foundation, Pierrefonds, Canada | [8]Perinatal Cardiology Consultants, Havertown, Pennsylvania, USA | [9]Clínica Angelman de Buenos Aires, San Isidro, Buenos Aires, Argentina | [10]The Angelman Network, Warkworth, New Zealand | [11]AngelmanUK, Nuneaton, UK | [12]RTI International, Raleigh, North Carolina, USA | [13]Boston Children's Hospital, Boston, Massachusetts, USA | [14]UCSD, Rady Children's Hospital San Diego, San Diego, California, USA | [15]COMBINEDBrain, Brentwood, Tennessee, USA

Correspondence: Terry Jo Bichell (terryjobichell@combinedbrain.org)

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ABSTRACT

Angelman syndrome (AS) is a severe genetic neurodevelopmental disorder with an estimated prevalence of 1:20,000. Life expectancy appears to be normal, however, data regarding lifespan in AS are scarce. Until 2018, there was no unique diagnosis code for AS, thus true incidence, prevalence, mortality and morbidity rates are unknown. A social media effort was launched by caregivers of people with AS to gather community-sourced data to understand AS mortality risks. Information on 220 deaths was verified with obituaries and public postings. Respiratory illness was the primary cause of death among people with AS overall, followed by accidents and seizures. Surprisingly, sudden unexpected death in sleep (SUDS) was the fourth most common cause, which has not been reported previously. Approximately 91% of people with AS have epilepsy, thus some SUDS cases may represent sudden unexpected deaths in epilepsy (SUDEP). Causes of death vary by age, and differ from the general population. Though there are obvious limitations to data collected through social media, grass roots science is a starting point to amass preliminary data and inform future epidemiological research on AS.

1 | Introduction

Angelman syndrome (AS) is a severe neurodevelopmental disorder caused by lack of functional UBE3A protein in neurons (Sutcliffe et al. 1997). There are four known molecular etiologies for AS: Deletion of the AS critical region on the maternal chromosome 15q11q13, paternal uniparental disomy (UPD) for chromosome 15, pathogenic variants in maternally inherited *UBE3A*, and imprinting defect (ID) of the maternal copy of *UBE3A* (Keute et al. 2021). Estimates of incidence range from 1:12,000 to 1:60,000 live births (Mertz et al. 2013; Petersen et al. 1995; Thomson, Glasson, and Bittles 2006). Causes of death in AS have not been previously researched, and the mortality rate of individuals with AS is unknown. AS is not included in any of the state newborn screening panels, and until 2018 there was no unique International Classification of Diseases (ICD) code for the disorder in the United States. Therefore, the true incidence, prevalence, and mortality rates for AS have been difficult to determine. A natural history study of AS was initiated in 2003 (Tan et al. 2011), and a global registry of AS individuals

was launched in 2016 (Napier et al. 2017), but neither of these efforts attempted to systematically collect data about deceased AS individuals or establish the cause of death in participants. The aim of the research reported here was to compile, for the first time, a list of deceased individuals with AS and to identify the cause of death in each case using all available data sources, including public notices, social media postings, and research registries.

Life expectancy among individuals with AS is assumed to be normal, but there have not been any studies examining the lifespan of individuals with AS. In a 1998 study of adults institutionalized for severe cognitive disability, of the 225 residents,11 were diagnosed with AS, ranging in age from 31 to 64 years (Buckley, Dinno, and Weber 1998), though it is important to note that these diagnoses were based on clinical, not genetic findings, and some of them may have been misdiagnosed as having AS. Adults as old as 83 have been identified (Krey et al. 2021), but there are likely to be many adults with AS who are undiagnosed because the etiology of AS was unknown until the chromosome 15 deletion was reported in 1987, and loss of *UBE3A* expression as the cause of AS was not identified until 1997 (Kishino, Lalande, and Wagstaff 1997; Matsuura et al. 1997). As such, individuals who have not had any genetic testing for AS since the late 1980s would not have had genetic confirmation of their diagnosis. In fact, molecular testing for variants in *UBE3A* was not available in clinical laboratories until after 1997. Nonetheless, there are reports in the literature regarding deaths of people with AS from drowning (Ishmael, Begleiter, and Butler 2002), seizures (King et al. 1996), filicide-suicide (Shields et al. 2015), mononucleosis (Herbst and Byard 2012), and respiratory arrest (Monterrubio-Villar and Córdoba-López 2008).

Due to the lack of an AS-specific ICD-10 code before 2018, it was impossible to systematically review vital documents, insurance databases, or hospitalization records to establish causes and rates of mortality among individuals with AS. Lacking a systematic way to study causes of death in children with AS, parents began to collect information through public postings and social media groups. After the use of listservs waned in the early 2000's, Facebook quickly became the most efficient way for families of individuals with rare disorders to connect and share concerns, anecdotes, and resources, as well as to recruit subjects for clinical trials. In 2010, a private Facebook group for families of people with AS was established, known as Angelman Connections, which has grown to more than 5700 members in over 30 countries. As of November 2022, there were more than 90 additional AS-based Facebook groups, including groups focused on specific subjects such as seizures, myoclonus, ketogenic diet, alternative therapies, non-deletion diagnoses, orthopedic problems, communication, educational advice, infancy, and adulthood.

In November 2013, a private Facebook group named "Sharing Causes of Mortality in Angelman Syndrome" was established specifically to catalog mortalities among individuals with AS worldwide (Bichell 2022). Members of the group were notified that the information gathered by the group would be used to catalog causes of death among people with AS, and would be verified by publicly available sources whenever possible. As of November 2022, this group included 477 immediate family members of people with AS who reported cases of death among acquaintances and relatives with AS, including information such as date of birth, date of death, location of death, name of deceased, cause or circumstances of death, and the molecular subtype, if known. The group administrators attempted to confirm these details by contacting the family of the deceased directly, or by locating a public obituary, death notice, or news report on each case.

The potential for social networking sites (SNS) to impact health has been explored and discussed in previous publications (Eytan et al. 2011; Randolph 2012). In 2014, a review which explored the use of SNS as a mode of collecting data for health research concluded that SNS can be useful for this purpose. (Alshaikh et al. 2014).

By combining data from the community with the cases collected by prospective registries, we identified 220 mortalities of people with AS: 211 deaths were reported from the members of the Facebook group "Sharing Causes of Mortality in Angelman Syndrome", six from the Global AS Registry, which is a web-based platform that collects data on individuals with AS through a series of online surveys answered by caregivers, and three mortalities from the Natural History Study (NHS), a longitudinal study which has been enrolling patients with AS and gathering their medical history since 2006.

2 | Methods

Editorial Policies and Ethical Considerations: Informed consent was not obtained for data collected from publicly posted sources about individuals who were already deceased, following guidelines for research on social media (Bhatia-Lin et al. 2019). However, to further protect privacy, all identifying information has been redacted from the data table, ie. last name, date of birth, date of death, city where death occurred, and source of information. Members of the Facebook group were notified that posted information would be utilized to compile AS mortality statistics. The Natural History Study (NHS) was approved by the Institutional Review Board at each study site. The Global AS Registry was reviewed and approved by the Mater Misericordiae Ltd. Human Research Ethics Committee (approval number EC00332). This research complied with relevant regulatory requirements.

Data was gathered from social media and community-based sources, as well as the AS NHS and the Global AS Registry. The cause of death was recorded as stated by family members or as quoted in publications and news reports. The reports that stated the cause of death vaguely as "sudden or unexpected" were categorized as "Unexpected". Those that stated "died in sleep" were categorized as "SUDS" (sudden unexpected/unexplained death during sleep), and those reporting "illness" were categorized as "Unspecified Illness" (Table S1).

The NHS is an observational, longitudinal study that has been enrolling individuals with a molecular diagnosis of AS of all ages since 2006 (Khan et al. 2019). Individuals can enroll at any age, and each participant is evaluated periodically in person or by telemedicine at one of the 10 study sites in North America.

Medical history pertinent to the study is obtained at each visit. While attempts were made to contact families for annual follow-up visits, some families are lost to follow up. As such, if a participant were to pass away during the study and the caregivers did not report the death to the investigators, this information would not be included in the participant's record.

The Global AS Registry is an online caregiver-reported observational study that has been collecting data since 2016 and contained information on 1,854 people with AS at the time of this study. Participants create an account by completing a short registration form which includes personal information, contact details, and AS genotype confirmed by curated genetic reports (Foundation for Angelman Syndrome Therapeutics 2022; Krey et al. 2021). Caregivers enter information about the clinical, developmental and behavioral characteristics of their family member with AS after completing a mandatory electronic informed consent form to confirm understanding of the purpose of the registry, the voluntary nature of the study and the collection, storage and usage of the data. The data curators attempt to contact participants to complete all surveys, however, as with the NHS, they are unable to determine causes of non-responses and some records are incomplete, or lost to follow-up.

A comprehensive descriptive analysis was performed to summarize the attributes of the data set, including key demographic information and the causes of death. Age categories were determined based on groupings previously described in AS (Tan et al. 2011; Khan et al. 2019; Keute et al. 2021; Willgoss et al. 2020) and on known AS phenotypes. For example, seizures most often onset prior to age 5, are generally controlled in school aged children (ages 6–12), but can reappear during adolescence (ages 13–18), and stabilize again in adulthood (ages 19–29), but research is lacking on adults over age 30 (Larson et al. 2015). These categories differ slightly from the age categories reported by the National Vital Statistics System (Ahmad, Cisewski, and Anderson 2022).

3 | Results

There were 220 deaths reported, from nineteen countries of residence (Figure 1a). Of those, the majority ($n = 186$), were reported from five English-speaking countries: United States ($n = 141$), United Kingdom ($n = 17$), Canada ($n = 14$), Australia ($n = 10$), and New Zealand ($n = 4$). There were 17 deaths reported from Spanish-speaking countries: Spain ($n = 5$), Argentina, ($n = 5$), Mexico ($n = 3$), Chile ($n = 2$), and 1 each from Cuba and Peru. There were seven deaths reported from France, 2 each from Germany, Ireland and Italy, and one death each was reported from Indonesia, China, Poland, and Switzerland.

The 220 reported deaths occurred between 1979 and 2022 (Figure 1c). The private Facebook group began collecting mortality reports in 2013, and an average of 13.8 deaths were reported for each year thereafter. Deaths occurring before 2013 were reported retrospectively, with 124 cases occurring between 1979 and 2012. Three of these deaths were reported as having occurred before 1997 when the *UBE3A* gene was identified as the cause of AS. Prior to 1999, most cases of AS would have been diagnosed clinically. A spike in reported deaths occurred in 2020, the first year of the COVID-19 pandemic.

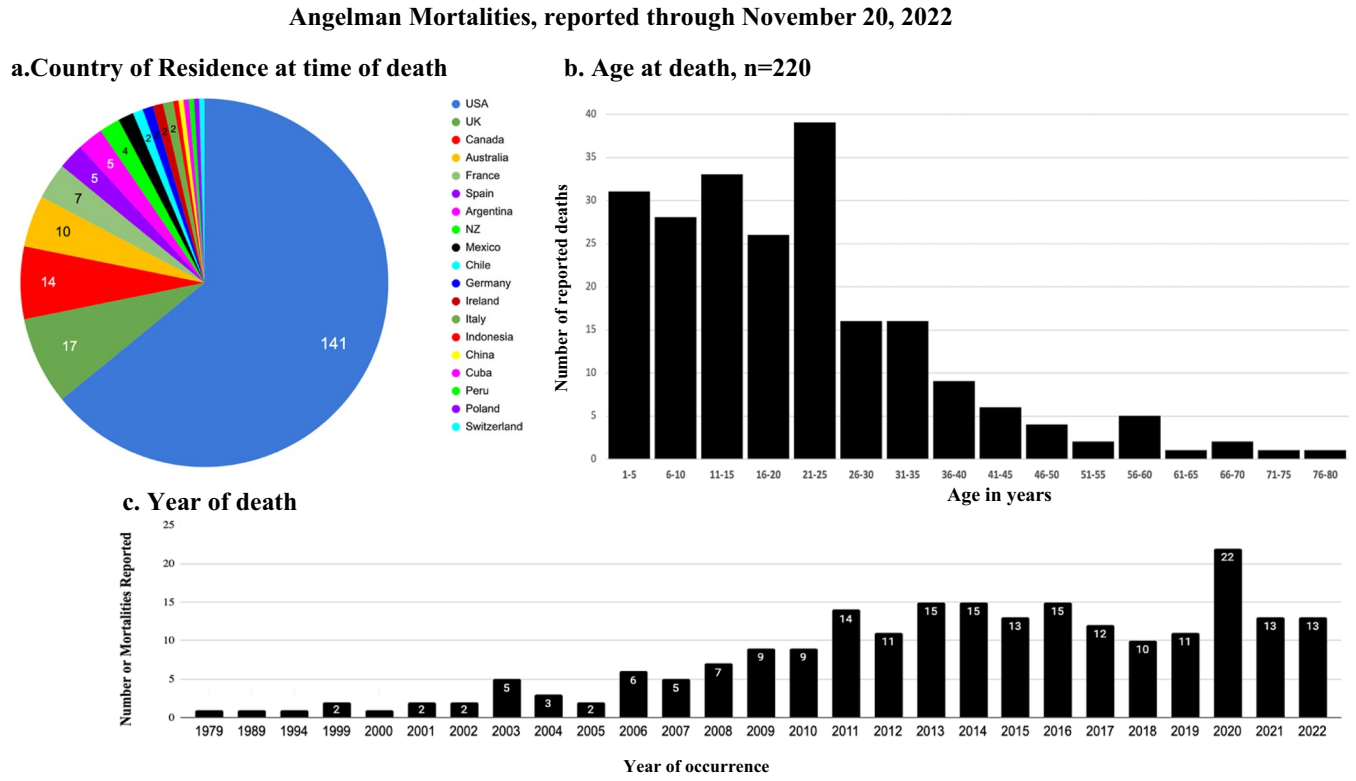

FIGURE 1 | Angelman mortalities reported through November 20, 2022 from community sources. (a) Country of residence at time of death. (b) Age at time of death. Range 1–78 years of age, median 18. (c) Year of occurrence of death. Range 1979–2022.

TABLE 1 | Reported causes of death in people with Angelman syndrome, by age group.

Cause of death	Ages 1–5	Ages 6–12	Ages 13–18	Ages 19–29	Ages 30+	Totals
Pneumonia/respiratory illness	3	5	5	14	5	32
Accidents	6	13	3	5	1	28
Seizures	7	5	0	9	2	23
Sudden unexpected death in sleep (SUDS)	2	3	5	3	4	17
Cancer	0	2	0	5	10	17
Post-operative complications	1	2	4	4	0	11
Homicide (Filicide)	1	0	3	2	0	6
Sepsis	0	2	2	0	0	4
Meningitis	0	2	0	0	0	2
Heart failure	0	1	0	0	1	2
COVID-19	0	0	0	1	1	2
Renal failure	0	0	0	0	2	2
Bowel perforation/obstruction	0	0	0	0	2	2
Unexpected death	0	0	1	0	0	1
Pancreatitis	0	0	0	0	0	0
Neurodegeneration	0	0	0	0	1	1
Pulmonary fibrosis	0	0	0	0	1	1
Unspecified illness	0	1	2	4	4	11
No cause listed	11	9	5	16	17	58
Totals	31	45	30	63	51	220

The age of death ranged from 1 to 78 years old, with a median age of 18 years (Figure 1b). Of the 220 cases collected, 150 had a reported cause of death (Table 1). The leading cause of death overall was pneumonia/respiratory illness ($n = 32$), followed by accidents ($n = 28$), seizures ($n = 23$), sudden unexpected death in sleep (SUDS) ($n = 17$) and cancer ($n = 17$).

The rank order of the causes of death varied by age. Among children aged 1–5 years, there were 31 cases of death, with seizures ($n = 7$) and accidents ($n = 6$) as leading causes. Accidents included one drowning, one suffocation on a school bus due to malpositioning in the seat, one peanut allergy anaphylaxis, one choking on a balloon, and two unspecified accidents. One child was drowned by a grandparent. Among deaths in which a cause was specified, sudden unexpected death in sleep (SUDS) was the cause of death in 7% of the cases ($n = 2$). Postoperative complications were reported as the cause of death in one case.

In children aged 6–12 years, there were 45 reported deaths, of which 36 reported a cause of death. Accidents ($n = 13$) were the leading cause of death in this age group: reported as drowning ($n = 8$), choking ($n = 1$), house fire ($n = 1$), car accident ($n = 1$), complications of fractured arm ($n = 1$), and suffocation in chair ($n = 1$). Seizures caused 5 deaths in this age group, and SUDS was reported in 3 cases (8% of deaths in which a cause was specified). Cancer caused 2 deaths (brain tumors, $n = 2$), as did postoperative complications ($n = 2$) and meningitis ($n = 2$).

In adolescents, 13–18 years old, there were 30 reported deaths, with 25 citing a cause. Among these, the leading causes were SUDS ($n = 5$, 25%), pneumonia ($n = 5$), and accidents ($n = 3$). There were no deaths attributed to seizures. Accidents included house fire ($n = 1$), heat stroke ($n = 1$), and choking during tube feed at school ($n = 1$). Four deaths were caused by postoperative complications, and two were caused by sepsis. Three adolescents died by filicide.

In young adults, aged 19–29 years, there were a total of 63 deaths, with 47 reporting a cause. Respiratory illnesses and pneumonia were the leading cause ($n = 14$), and COVID-19 caused one death. Seizures ($n = 9$) were more common than accidents ($n = 5$) as the cause of death in this age group. Cancer was the third leading cause of death in young adults ($n = 5$), with 3 of these specified as ovarian ($n = 1$), leukemia ($n = 1$) and lymphoblastic leukemia ($n = 1$). Postoperative complications were reported as the cause of death in four cases, and SUDS was reported in three cases (6% of deaths with a reported cause). Accidents in this age group included choking on food ($n = 2$), house fire ($n = 1$), elopement ($n = 1$), and head trauma ($n = 1$). Two young adults died by filicide.

In adults over age 30, there were 51 deaths, of which 34 had a reported cause. In this age group, cancer was the leading cause of death ($n = 10$). Types of cancers included colon ($n = 3$), lymphocytic leukemia ($n = 2$), lymphoma ($n = 1$), liver ($n = 1$), brain

($n=1$), breast ($n=1$) and unspecified adenocarcinoma ($n=1$). Pneumonia was the second leading cause of death in adults over 30 ($n=5$), with at least one additional death caused by COVID-19. SUDS was the cause of four deaths (12% of those with a reported cause). Two cases were reported to have died from seizures, two from bowel perforation/obstruction, and two from renal failure. One death was due to heart failure, one to pulmonary fibrosis and one to neurodegeneration. There was only one death due to an accident in this age group, caused by a fall.

In addition to the 211 mortalities reported through community-based sources, nine deaths were recorded by the NHS and the Global AS Registry and were included in the total (Table 1). Three of these deaths were reported by the NHS (Table 2), of which two were due to drowning and one was listed as asphyxiation.

Six deaths were recorded by the Global AS Registry (Table 3), of which two were caused by respiratory illness and pneumonia, one was due to a protracted seizure, and three had no cause cited.

4 | Discussion

There were 220 mortalities among people with AS reported from all available sources through November 2022. Of these, no cause of death was discoverable for 58 cases, and 12 cases were reported to be caused by "Unspecified illness" ($n=11$) or "Unexpected death" ($n=1$). Among the 150 cases with a reported cause of death, the overall causes of death in rank order were: (1) respiratory illnesses, (2) accidents, (3) seizures, (4) SUDS, (5) cancer, (6) post-operative complications, and (7) filicide. Each of these sources of mortality in AS are discussed below.

TABLE 2 | Angelman Syndrome Natural History Study, mortalities.

	Age at death	Genetic diagnosis	Cause of death
Case 1	10 years	Class 2 deletion	Water inhalation asphyxiation
Case 2	13 years	Class 2 deletion	Was found unresponsive. Was told cause was asphyxiation
Case 3	10 years	Class 2 deletion	Accidental drowning

4.1 | Respiratory Illnesses

Respiratory illnesses and pneumonia (grouped together) were the leading cause of death overall for all individuals with AS, and the leading cause of death in young adults with AS (Neligan et al. 2011). Additionally, it is possible that the category "Post-operative complications" ($n=11$) may have included some cases of pneumonia or sepsis (as has been recently described following scoliosis surgery; Winsauer et al. 2023). Some of these cases may have been caused by COVID-19. This finding is consistent with many studies that reported a high risk of respiratory-related deaths in individuals with intellectual disabilities (Truesdale et al. 2021), and represents a significant departure from causes of death in the general population, in which respiratory disease is the 6th leading cause of death, and remained so even during the COVID-19 pandemic (Xu et al. 2022). Given the high prevalence of dysphagia in individuals with learning disabilities (Weir et al. 2011), it is essential to recognize that aspiration pneumonia may represent a significant portion of the cases of respiratory illnesses and pneumonia.

Though at least seven cases of illness from COVID-19 among individuals with AS were collected from citizen scientists combing social media posts in 2020, only one fatality was recorded as of December 2020 before vaccinations were available, and one in 2021. However, delaying medical care during the COVID-19 pandemic may have contributed to the uptick in the number of deaths from causes other than COVID-19 in 2020 and 2021.

4.2 | Accidents

Accidents were the second leading cause of death overall for people with AS, and the leading cause in school-aged children (6–12 years old). Because of the behavioral profile that includes fascination with water, and the ability of most school-aged children with AS to ambulate, access to bodies of water is an anticipated source of risk for people with AS (Ishmael, Begleiter, and Butler 2002), and indeed, drownings were the most common accidental cause of death in school-aged children ($n=8$). However, in the general population, drowning is also the leading cause of death from unintentional injury for those aged 1–5 years and the second leading cause for children aged 0–17 years (Ahmad, Cisewski, and Anderson 2022). In adolescents and young adults, there were no accidental drownings.

Head trauma ($n=1$) was the accidental cause of death in adults. The gross motor profile in AS includes impaired balance due to

TABLE 3 | Global Angelman Syndrome Registry, mortalities.

	Age at death	Location	Genetic diagnosis	Cause of death
Case 1: Male	29	USA	Not available	Pneumonia for several weeks prior to passing
Case 2: Male	29	Australia	Not available	Hospitalized, no cause given
Case 3: Female	10	Australia	Not available	Respiratory distress, multiple organ failure, sepsis
Case 4: Male	Born 2000	Mexico	Deletion positive	Oxygen dependent, had 24 h seizure that required sedation
Case 5: Male	Born 2004	Australia	Deletion positive	Cause not reported; also had juvenile arthritis
Case 6: Male	Born 2016	Poland	Not available	Cause not reported

uncoordinated movement patterns, commonly associated with ataxic-like gait, mild or moderate spasticity and abnormal muscle tone (Petkova et al. 2022), and motor impairments in AS likely contribute to an increased risk of trauma sustained in falls.

4.3 | Seizures

Seizures were the third most common cause of death overall ($n = 23$). The prevalence of epilepsy in AS is estimated to be between 61% and 91% for non-deletion versus deletion type (Weir et al. 2011). It is recognized that people with epilepsy are at higher risk for premature death, and these reports of epilepsy-related deaths raise the question of whether better seizure control, which may or may not be possible in some of these individuals, might reduce the risk of premature death (DeGiorgio et al. 2020).

4.4 | Sudden Unexpected Deaths (SUDEP)

Additionally, the categories "Sudden Death in Sleep" and "Unexpected Death" might be related to Sudden Unexpected Deaths in Epilepsy (SUDEP), which is defined as the sudden and unexpected, non-traumatic and non-drowning death of a person with epilepsy without a toxicological or anatomical cause detected at the post-mortem examination (Nashef et al. 2012). Though three of the SUDS deaths were attributed to SUDEP, it is not possible to determine from the data reported herein if any of the remaining cases of SUDS fit the definition of SUDEP (because information is lacking on whether the deceased individual had epilepsy, and whether any other cause of death was sought or found on post-mortem examination). However, given the extremely high prevalence of seizures in AS (Pelc et al. 2008) it is likely that at least some of the cases described herein as SUDS ($n = 14$) are indeed SUDEP. Though SUDEP has not previously been reported in AS, it is known to be a risk among people with duplication of the same chromosomal region (chromosome 15q11q13) that is deleted in 70% of individuals with AS (Friedman et al. 2016). In 2023, Donnan et al. reported 20 cases of SUDEP among 510 individuals with developmental and epileptic encephalopathies, none of which occurred in patients with AS, though the number of AS patients in the cohort ($n = 19$) was not large enough to conclude that SUDEP is rare in AS (Donnan et al. 2023).

4.5 | Cancer

Among adults with AS, cancer was the leading cause of death ($n = 10$), and "Unspecified Illness" may have included some additional cancer diagnoses. There was no dominant type of cancer, and deaths due to cancer in AS included cases of leukemia as well as carcinomas of the colon, brain, breasts, and ovaries. This underscores the need for individuals with AS to undergo standard cancer screening as recommended for the general population.

4.6 | Filicide

Perhaps most disturbing was filicide ($n = 6$) as the seventh most common cause of death; this category could be over-represented, as some data sources, such as public websites and news reports, might include more crimes and accidents than vital document data. Filicides were committed by grandparents, parents or step-parents, and suicide often accompanied the filicide, with methods that included strangulation, drowning, intentional house-fires, and overdoses. This could represent extreme cases associated with caregiver stress, which is elevated in families of AS individuals (Miodrag and Peters 2015; Wheeler, Sacco, and Cabo 2017). Caregivers report high levels of fatigue, adverse effects on their social life, increased irritability, and arguments with partners. This is even more evident for those with sleep disturbances, which is a common comorbidity in AS patients (Miodrag and Peters 2015; Wheeler, Sacco, and Cabo 2017).

4.7 | Overall

In the general population in 2021, the leading causes of death overall were heart disease, cancer, COVID-19 infection, and unintentional injury (largely driven by drug overdose deaths) Drug Overdose Death Rates 1999–2021 (2023), followed by stroke, respiratory illness, Alzheimer disease, diabetes, liver disease, and kidney disease, in that order (Xu et al. 2022). Similarly, in the AS population, cancer and unintentional injuries or accidents are within the five leading causes of death overall, but the ranking is quite different from the typical population, especially in the case of seizures, SUDS, post-operative complications, filicide, sepsis, meningitis, and heart failure (Ahmad, Cisewski, and Anderson 2022). Much of this may be due to the lack of diagnosed AS cases in adults over 30 years of age and thus the limited number of mortalities reported in older adults.

4.8 | Limitations

It is important to note when comparing the Global AS Registry, NHS data and community-sourced data, that the numbers of occurrences are remarkably different between the groups, with only three reports coming from the NHS, six from the Global AS Registry and 211 cases reported through the Facebook group. This is most likely not only due to the total population that each source draws from, but also due to the main purpose of those sources; neither the NHS nor the Global AS Registry specifically aim to collect mortality information.

The community-sourced data compiled for this publication were gleaned by citizen scientists, who combed published reports and public postings about deaths of people with AS. These data have obvious limitations, including the subjective nature of the causes of death reported, and the lack of secondary and tertiary causes of death. Many of the cases listed in the table are missing key data elements despite attempts to obtain as many details as possible through the available avenues. The lack of verifiable genetic records is a shortcoming, as some individuals diagnosed clinically with AS may have had other diagnoses. There is bias toward North America, as most data were gathered in English-language social media posts, and through published obituaries, which are culturally uncommon in many countries, and becoming less common in general. Facebook

itself is waning in popularity among younger parents, who are moving to Instagram and other social media platforms, which are more difficult to monitor in the aggregate. Most importantly, because the ICD-10 code for AS was only approved in 2018, the lack of long-term verifiable ICD-based data on incidence and prevalence of AS impedes current attempts to quantify life expectancy, morbidities, and mortality for the disorder.

These community-sourced data highlight the need for a systematic exploration of the morbidity and mortality risks faced by individuals with AS. As the unique diagnosis code for AS in ICD-10 (Q93.51) becomes commonly applied in hospitalization records and death certificates, more rigorous study of the subject may be possible. Prospectively collected data through registries and natural history studies will allow risk estimates, particularly if ethics committees permit future contact of families of enrolled subjects to obtain medical records and death certificates. If AS is included in newborn screening programs, true incidence and prevalence will be calculable, and the actual epidemiology and mortality risks may be established.

5 | Conclusions

Compared to the general population, the causes of mortalities in people with AS were skewed towards respiratory illnesses, seizures, SUDS (possibly SUDEP), post-operative complications, and filicide. A high prevalence of gastroesophageal reflux disease (GERD) in patients with AS (Leader et al. 2022) suggests an underlying factor that may contribute to both respiratory infection from aspiration (Weir et al. 2011) and SUDS/SUDEP (Mandal et al. 2021). The standard of care for AS should include attention to prevention of these mortality risks. More systematic research on the epidemiology of AS is required to understand and prevent causes of death across the lifespan.

Author Contributions

Adriana T. Gomes: formal analysis, writing original draft, review and editing. **Amanda Moore:** data collection and curation, writing review and editing. **Meagan Cross:** data collection and curation, writing review and editing. **Cristy Hardesty:** data collection and curation. **Kelly David:** data collection and curation, writing review. **Maria Galan Sampedro:** data collection and curation. **Sophie Dube:** data collection and curation. **Sharon Weil-Chalker:** data collection and editing. **Adela Gentil Montepagano:** data collection and curation. **Ursula Christel:** data collection and curation. **Rachel Martin:** data collection and curation. **Anne Wheeler:** data review and editing. **Wen-Hann Tan:** data collection and curation, writing, review and editing. **Lynne M. Bird:** data collection and curation, writing, review and editing. **Terry Jo Bichell:** conceptualization, project administration, data collection and curation, formal analysis, writing original draft, review and editing.

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Ethics Statement

Informed consent was not obtained for data collected from publicly posted sources about individuals who were already deceased, however all identifying information has been redacted from the data table, ie. last name, date of birth, date of death, city where death occurred, source of information. The NHS was approved by the Institutional Review Board at each study site. The Global AS Registry was reviewed and approved by the Mater Misericordiae Ltd. Human Research Ethics Committee (approval number EC00332).

Conflicts of Interest

A.G., A.M., M.C., C.H., K.D., M.G.S., S.D., S.W.-C., A.G.M., U.C., R.M. declare no conflicts of interest. A.W. is an unpaid voluntary member of the Angelman Syndrome Foundation Scientific Advisory Board, and a paid consultant with Ionis Pharmaceuticals to advise on the conduct of clinical trials for Angelman syndrome. W-H.T is an unpaid voluntary member of the Angelman Syndrome Foundation Scientific Advisory Committee. W-H.T is an investigator being paid to conduct clinical trials in Angelman syndrome (F. Hoffman-LaRoche, Ultragenyx, Ionis Pharmaceuticals). L.M.B is a paid consultant with Ionis Pharmaceuticals to advise on the conduct of clinical trials for Angelman syndrome. L.M.B is a principal investigator being paid to conduct clinical trials in Angelman syndrome (F. Hoffman-LaRoche, Ultragenyx, Ionis Pharmaceuticals). T.J.B was a participant on Angelman patient advisory council at Hoffman LaRoche (2019–2023).

Data Availability Statement

The data that supports the findings of this study are available in the supplementary material of this article. First names, last names, date of birth, date of death, city of residence at death, and link to obituaries and public postings have been removed to de-identify the deceased.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.