Mortality From Neurodegenerative Diseases in a Cohort of US Flight Attendants

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Background *Concern exists about the potential chronic neurological effects among aircrew of exposure to chemical contaminants from engine oil in aircraft cabin air. We evaluated mortality from neurodegenerative diseases among 11,311 former US flight attendants.*

Methods *Vital status was ascertained through 2007, and life table analyses were conducted to obtain standardized mortality ratios (SMRs).*

Results *Amyotrophic lateral sclerosis (ALS) mortality was over twice as high in the cohort as in the US general population, based on nine observed ALS deaths. There was no clear pattern in risk when SMRs for ALS were stratified by exposure duration. Mortality from other neurodegenerative diseases was not elevated.*

Conclusions *Our findings are limited due to small numbers of observed deaths and reliance on mortality data, but suggest that flight attendants may have an increased risk of ALS. Additional research is needed.* Am. J. Ind. Med. Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

KEY WORDS: flight attendants; ALS; neurodegenerative diseases; mortality; cohort

INTRODUCTION

During most commercial aircraft flights, heated and conditioned engine air is cooled and supplied unfiltered to the aircraft cabin. This air can become contaminated with pyrolyzed engine lubricating oils and hydraulic fluids through leaking oil seals or bearings, ruptured fluid lines, improper maintenance, or other malfunctions [NRC, 2002]. Estimates of the frequency of such air contamination events range from 1 in 100 flights to 1 in 22,000 flights [NRC, 2002; Winder, 2006; COT, 2007]. Neurological and other symptoms that are temporally related to these events on aircraft have been reported [Montgomery et al., 1977; Parliament of the Commonwealth of Australia, 2000; NRC, 2002; Ross, 2008]. In a case study of air contamination events at a major US airline, at least one crew member developed symptoms serious enough to require emergency medical care in over half of the events; some crew members developed chronic neurological symptoms [Murawski, 2011]. Several cohort studies of aircrew have been conducted, but neurodegenerative disease mortality has not been reported in these studies. In a proportional mortality study of US pilots and navigators, motor neuron disease mortality was elevated [Nicholas et al., 1998].

Some investigators have hypothesized that the symptoms reported by aircrew are related to exposure to tri-cresyl phosphate, an anti-wear additive in jet-engine oils [Parliament of the Commonwealth of Australia, 2000]. Tri-cresyl phosphate is an organophosphate and a known neurotoxicant. Aircrew are also potentially exposed to pesticides

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which have been linked, in some studies, to neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) [Kamel et al., 2012; Malek et al., 2012].

Because of concern about possible chronic neurological effects from air contamination events in aircrew, we evaluated mortality from neurodegenerative diseases among a cohort of former flight attendants who worked for Pan American World Airways (Pan Am), a large, US-based international airline that ceased operations in December 1991 [Pinkerton et al., 2012]. An earlier study of this cohort did not specifically evaluate mortality from neurodegenerative diseases.

MATERIALS AND METHODS

The cohort, assembled from personnel records of Pan Am, includes 11,324 former employees who were employed for at least 1 year as a flight attendant, were US citizens when they were hired, and who worked at least 1 day after January 1, 1953 [Pinkerton et al., 2012]. For cohort members who transferred to Pan Am when Pan Am bought National Airlines in 1981, the time employed as a flight attendant at National was counted towards the 1-year minimum. Employment duration as a flight attendant at Pan Am and National excluding training and adjusted for part-time work was used as an exposure surrogate.

Vital status was previously ascertained through 2007 [Pinkerton et al., 2012]. All deaths were coded according to the International Classification of Diseases (ICD) in effect at the time of death. ALS, Parkinson's disease, cerebrovascular dementia, and non-cerebrovascular dementia (including Alzheimer's disease) were identified from the ICD codes as indicated in Table I. Mortality was analyzed using a life-table analysis program, LTAS.NET [Schubauer-Berigan et al., 2011]. US population mortality rates (beginning on January 1, 1960) were created from National Center for Health Statistics mortality data and US census population estimates. Cohort members with a missing birth date (n = 1) or who were last observed prior to the rate file begin date (n = 12) were excluded from all analyses. Person-years at risk (PYAR) began at the latest of the rate file begin date, the date the 1 year eligibility period was met, or, for flight attendants who transferred to Pan Am from National, the date of transfer from National. PYAR ended at the earliest of the date of death, the date last observed in the United States, or the study end date (December 31, 2007). A few cohort members only accumulated PYAR until the date last employed because they were lost to follow-up (n = 60) or lived outside of the United States after they stopped working for Pan Am (n = 63). The PYAR were stratified into 5-year intervals by age and calendar time and multiplied by the appropriate gender and race-specific mortality rates to calculate the expected number of deaths. The ratio of the observed to the total expected number of deaths was expressed as the standardized mortality ratio (SMR), and 95% confidence intervals (CIs) were calculated assuming that the number of observed deaths follows a Poisson distribution. SMRs were stratified by employment duration and time since first employment. Time since first employment was considered because of the possibility of a long latency period between exposure and the manifestation of disease.

TABLE I. The International Classification of Diseases (ICD) Codes Mapped to Each Neurodegenerative Disease Death Category by ICD Revision

Cause of death category	ICD-7 code	ICD-8 code	ICD-9 code	ICD-10 code
ALS[a]	356.1	348.0	335.2	G12.2
Parkinson's disease	350	342	332, 332.0–332.1	G20 G21
Cerebrovascular dementia	306	293.0–293.1	290.4	F01
Non-cerebrovascular dementia (including Alzheimer's disease)	304–305	290.0–290.1	290.0–290.3 331.0	G30

ALS, amyotrophic lateral sclerosis.
[a]The ICD-7 and ICD-8 codes are specific for ALS. For deaths that occurred when ICD-9 and ICD-10 were in effect, ICD codes specific for ALS were not available, and codes for motor neuron disease were used to identify deaths that may be due to ALS.

Analyses were conducted based on underlying cause of death and on multiple causes of death in which all causes of death on the death certificate are considered [Steenland et al., 1992]. Multiple cause of death analyses were conducted because some neurodegenerative diseases (e.g., Alzheimer's disease, Parkinson's disease) are listed on many death certificates as a contributing cause and not as the underlying cause of death [Redelings et al., 2006]. The results presented are for analyses based on underlying cause of death unless otherwise indicated. The study was approved by the National Institute for Occupational Safety and Health Institutional Review Board.

RESULTS

The study included 11,311 former flight attendants contributing 350,771 PYAR. Cohort members were predominantly white females (76.2%) (Table II). The median employment duration was 5.9 years, and median time since first employment was 35.8 years. Only 4% of the cohort was employed prior to 1953, when the study period began. About 9% of the cohort was deceased; the mean age at death among cohort members who died in the United States was 57.1 years (standard deviation [sd] = 15.2). The mean age at the end of

TABLE II. Characteristics of the Study Population

Characteristic	No.	%
Excluded from analysis[a]	13	
Number of workers	11,311	
Race/sex		
White male	1,503	13.3
Male other than White	198	1.8
White female	8,621	76.2
Female other than White	989	8.7
Vital status (as of 12/31/2007)		
Alive	9,953	88.0
Deceased[b]	1,022	9.0
Lost to follow-up[c]	336	3.0
Employment duration (years)[d]		
<5	5,085	45.0
5–<15	4,001	35.4
15+	2,225	19.7
Time since first employment (years)[d]		
<30	4,173	36.9
30–<40	4,040	35.7
40–<50	2,517	22.3
50+	581	5.1

[a]Cohort members were excluded when birth date was missing (n = 1) or when the date last observed was prior to 1960 (n = 12).
[b]Deaths from 1960 to 2007.
[c]Includes 23 cohort members who died outside of the United States and were considered lost to follow-up at the date last observed in the United States or, for flight attendants who did not live in the United States after they stopped working for Pan Am, the date last employed.
[d]Based on employment as a flight attendant at Pan Am and National excluding training and adjusted for part-time work.

follow-up for the remaining cohort members was 57.4 years (sd = 9.7).

A significant 2.21-fold excess in ALS mortality was observed in the cohort compared with the US general population, based on nine observed ALS deaths (Table III). Seven of the nine ALS decedents were female. The mean age of death for cohort members who died from ALS was 67.0 years (sd = 9.4). Mortality from other neurodegenerative diseases was not elevated.

There was no clear pattern in risk when SMRs for ALS were stratified by employment duration (Table IV). All 9 ALS deaths occurred among person-time 30 or more years since first employment. Among person-time 50 or more years since first employment, a significant 8.87-fold excess in ALS mortality, based on three observed deaths, was observed.

No additional ALS deaths were identified when all causes on the death certificate were considered. Some additional deaths from other neurodegenerative diseases were identified when all causes on the death certificate were considered. However, when the analyses were repeated based on multiple causes of death, SMRs for neurodegenerative diseases other than ALS remained less than one (data not shown).

TABLE III. Mortality From Neurodegenerative Diseases Among US Flight Attendants, 1960–2007

Cause of death	Obs	Exp	SMR (95%CI)
Neurodegenerative diseases combined	17	16.08	1.06 (0.62–1.69)
ALS	9	4.07	2.21 (1.01–4.20)
Parkinson's disease	3	3.66	0.82 (0.17–2.39)
Cerebrovascular dementia	0	0.45	0 (0–8.14)
Non-cerebrovascular dementia	5	7.90	0.63 (0.21–1.48)

ALS, amyotrophic lateral sclerosis; Obs, observed number of deaths based on underlying cause; Exp, expected number of deaths based on US referent rates; SMR, standardized mortality ratio; CI, confidence interval.

DISCUSSION

We observed a significant increase in ALS mortality in a cohort of flight attendants compared with the US general population. However, this finding was based on few observed ALS deaths and there was no clear pattern related to employment duration. The findings may be due to occupational exposures, other risk factors for ALS, or chance.

Flight attendants are potentially exposed to tricresyl phosphate, an organophosphate, and other contaminants in cabin air from pyrolyzed engine oils and hydraulic fluids. Engine lubricating oils contain 2–6% tricresyl phosphate by weight [Hecker et al., 2009]. Hydraulic fluids contain other organophosphates, such as butyl phosphates [Solbu et al.,

TABLE IV. ALS Mortality by Employment Duration and Time Since First Employment Among US Flight Attendants, 1960–2007

	Obs	Exp	SMR (95%CI)
Employment duration, years[a]			
<5	4	1.48	2.70 (0.73–6.90)
5–<15	2	1.28	1.56 (0.19–5.63)
15+	3	1.30	2.30 (0.48–6.73)
Time since first employment, years[a]			
<30	0	1.15	0.00 (0.00–3.21)
30–<40	3	1.60	1.88 (0.39–5.49)
40–<50	3	0.99	3.04 (0.63–8.88)
50+	3	0.34	8.87 (1.83–25.92)

ALS, amyotrophic lateral sclerosis; Obs, observed number of ALS deaths based on underlying cause; Exp, expected number of ALS deaths based on US referent rates; SMR, standardized mortality ratio; CI, confidence interval.
[a]Based on employment as a flight attendant at Pan Am and National excluding training and adjusted for part-time work.

2010]. Some, but not all, hydraulic fluids have also contained tricresyl phosphate [van Netten, 2000; van Netten and Leung, 2001; Hecker et al., 2009; Solbu et al., 2010]. Tricresyl phosphate is a known neurotoxicant. The isomers of tricresyl phosphate vary in toxicity, with ortho-cresyl isomers considered to be the most toxic [Craig and Barth, 1999]. In 1930, thousands of Americans developed limb paralysis after drinking "Jamaica ginger" adulterated with tri-ortho-cresyl phosphate. On follow-up, some victims later developed an upper motor neuron syndrome related to ALS [Morgan and Penovich, 1978]. Other outbreaks due to accidental ingestion have been reported as well [Morgan, 1982]. Few reports of neurologic effects from exposure presumably resulting from inhalation or dermal contact have been reported in workers other than aircrew [Craig and Barth, 1999], and it is unclear whether inhalational exposure to tricresyl phosphate resulting from air contamination events could lead to frank neurotoxicity [NRC, 2002].

All 9 ALS deaths in this study occurred 30 or more years after first employment. The potential for neurotoxicity from tricresyl phosphate during air contamination events may have been greater in the past because manufacturers reduced the levels of ortho-cresyl isomers of tricresyl phosphate to address this issue [NRC, 2002; Winder and Balouet, 2002].

Flight attendants are also exposed to pesticides. Potential exposure to flight attendants occurs from personally applying pesticides after the plane leaves the gate and/or before it lands and from residual applications by ground crew prior to passenger and aircrew boarding [Sutton et al., 2007]. Many pesticides are recognized neurotoxicants. In addition, pesticides have been implicated in ALS [Kamel et al., 2012; Malek et al., 2012]. In the Agricultural Health Study, ALS was associated, although not significantly, with the use of organochlorine insecticides, pyrethroids, herbicides, and fumigants as well as the following specific organochlorines: aldrin, dieldrin, DDT, and toxaphene [Kamel et al., 2012]. Currently, synthetic pyrethroids are used on commercial aircraft [World Health Organization, 1995; NRC, 2002; Sutton et al., 2007] to comply with the disinsection requirements of at least 23 countries for some or all in-bound flights [US Department of Transportation, 2015]. Aircraft flown to and from destinations requiring disinsection may also be used on other routes. Other pesticides including DDT were used historically [Ellis, 1996].

We were unable to evaluate whether ALS mortality was associated with exposure to tricresyl phosphate or other contaminants in oil fumes or pesticide exposure because we had no data on air contamination events or occupational pesticide exposure. Air contamination events are transient and their frequency may vary depending on aircraft type while pesticides are only applied to aircraft for specific flights, depending on the requirements of the destination country [NRC, 2002]. Thus, employment duration is probably a poor surrogate for exposure to pesticides and exposures related to air contamination events. Working conditions and scheduling of flight attendants have changed considerably over time. Employment duration was also based on employment at Pan Am and National and did not include employment at other airlines. In addition, the power to detect an association with exposure was low due to the small number of observed ALS deaths and the relatively low median employment duration of cohort members. If, based on other data, we assume that flight attendants worked on 280 flights per year [Grajewski et al., 2015] and that air contamination events occurred on between 1 in 100 and 1 in 22,000 flights, we estimate that a flight attendant employed for 5.9 years (the median employment duration in our study) would have been exposed to between 0 and 16 air contamination events.

We had no data on smoking, a risk factor for ALS [Gallo et al., 2009]. However, mortality from lung cancer and chronic obstructive pulmonary disease in the cohort was less than expected compared to the US general population [Pinkerton et al., 2012], which suggests that differences in smoking and exposure to environmental tobacco smoke between the cohort and general population may have biased the overall SMR for ALS towards the null but were unlikely to have biased the overall SMR for ALS away from the null.

Another limitation is our reliance on mortality data. ALS is fatal with a median survival of approximately 3 years [Czaplinski et al., 2006] making mortality a good surrogate of the incidence of ALS. However, mortality may be a poor outcome measure for other neurodegenerative diseases. In a study of 450 subjects with dementia who died between 1988 and 1990, the sensitivity of death certificates compared to medical record diagnoses for Alzheimer's disease, senile or presenile dementia (which are included in the non-cerebrovascular dementia death category), and cerebrovascular dementia was 28%, 15%, and 8%, respectively [Macera et al., 1992]. In another study, the sensitivity of death certificates compared to self-report was 54.8% for Parkinson's disease [Pressley et al., 2005]. This may have adversely affected our ability to detect an elevation in neurodegenerative diseases other than ALS, if an elevation exists.

Another limitation was the lack of ICD codes that are specific for ALS in ICD-9 and ICD-10, necessitating use of the code for motor neuron disease to identify cohort members and individuals in the general population who may have died from ALS when these revisions of the ICD were in effect. All nine deaths that were mapped to ALS occurred when ICD-10 was in effect. According to the death certificates, seven of these deaths were due to ALS; two were due to progressive supranuclear palsy. Although progressive supranuclear palsy is not a motor neuron disease, a separate study that evaluated the accuracy and usefulness of ICD-10 codes to identify ALS found that progressive supranuclear palsy was commonly coded as motor neuron disease [Stickler et al., 2012]. We did not conduct analyses of ALS excluding the two deaths due to

progressive supranuclear palsy so that the cohort data would be comparable to the general population data.

Our ability to detect an elevation in neurodegenerative diseases was also limited by the relatively young age of the cohort. In addition, some flight attendants who were lost to follow-up may have left work due to illness. However, loss to follow-up was low, and most cohort members who were lost to follow-up last worked before the typical age of onset of ALS and other neurodegenerative diseases evaluated in this study. Thus, it seems unlikely that loss to follow-up led to substantial bias in the risk estimates.

Our findings are consistent with a proportional mortality study of US commercial pilots and navigators which found a significant increase in mortality from motor neuron disease, based on eight observed motor neuron disease deaths [Nicholas et al., 1998]. If our findings are replicated in other mortality studies, additional research may be needed to evaluate the potential role of air contamination events and other occupational exposures aboard commercial aircraft. In addition, studies evaluating neurological signs and symptoms among aircrew might provide additional insight into the potential for chronic neurological effects from occupational exposures to aircrew. However, designing and conducting rigorous studies is challenging due to the transient and unpredictable nature of air contamination events in aircraft. As a result, some researchers are focusing on identifying biomarkers of exposure and effect for tri-ortho-cresyl phosphate [Schopfer et al., 2010; Liyasova et al., 2011; Johnson et al., 2015]. However, this approach may be limited by differences in the concentration of various isomers of tricresyl phosphate in engine oils. Concern also exists about other components of pyrolyzed engine oils [Anderson, 2014; Michaelis, 2014]. Nonetheless, fully validated biomarkers of exposure to tricresyl phosphate and other components of pyrolyzed engine oil and hydraulic fluids that could be used in future epidemiologic studies may allow investigators to more accurately evaluate the association of neurodegenerative diseases with exposure to tricresyl phosphate or other exposures from air contamination events among aircrew.

AUTHORS' CONTRIBUTION

LEP and MJH participated in the design of the study. LEP also participated in the data collection and wrote the first draft of the manuscript. MJH analyzed the data. All authors participated in the interpretation of data, critically reviewed manuscript drafts, and approved the final manuscript.

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ETHICS REVIEW AND APPROVAL

The study was approved by the Institutional Review Board of the National Institute for Occupational Safety and Health.

DISCLOSURE BY AJIM EDITOR OF RECORD

Rodney Ehrlich declares that he has no competing or conflicts of interest in the review and publication decision regarding this article.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health or the Florida Department of Health.

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