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Research Project:

Age Limitations

Commercial Air Transport Pilots

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Age Limitations Commercial Air Transport Pilots

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Executive Summary

Project: Age Limitations Commercial Air Transport Pilots

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This Executive Summary is aimed at providing a summary of the following separate reports that are included in the present final document:

1. Part 1. Literature review and gathering of available data;
2. Part 2. Risk Assessment Based on Operations Considerations;
3. Part 3. Screening of Cardiovascular Risks in Asymptomatic Pilots;
4. Part 4. Conclusions and Recommendations.

For detailed information the reader is referred to the above-mentioned reports. The references mentioned in this Executive Summary are provided in the related reports.

Background

The current age limitations for commercial air transport pilots (CAT) required by Regulation (EU) No 1178/2011 were taken over from ICAO Annex 1. For single-pilot CAT operations the limiting threshold is the age of 60 and in multi-pilot CAT operations, pilots can continue to operate until the age of 65. These age limits were developed by the Agency without conducting a specific impact assessment on safety, health or social issues. A recent study (Müller et al., 2014) on the effects of aging pilots on safety of helicopter flights (the emergency medical service - HEMS - operations) has raised questions by a number of stakeholders and some Member States have already been granted exemptions under Article 14.4 of Regulation (EC) No 216/2008 for commercial single-pilot operations for pilots over 60 in HEMS operations. The scope of the study by Müller et al. is considered to be too narrow to provide a complete risk assessment for increasing the current age limitations for pilots in commercial air transport (CAT). A more systematic study is therefore required to extend the scope to the European level and to include pilots involved in different types of CAT operations.

Project description and general objectives

This study aimed to assess the possible need to mitigate the risk to flight safety resulting from the potential increasing cases of sudden incapacitation for pilots aged over 60. Furthermore, considering the different types of CAT operations the study will determine whether the potential risk of incapacitation can be mitigated by specific health screening or shortened screening intervals rather than by an age limit. In the case of a positive answer, the study will also propose a battery of tests (medical, physiological, psychological, etc.) to support aeromedical decision on the applicant's fitness on an individual basis. The research project will develop medical references related to the risk of pilot incapacitation in aviation environment taking into consideration the age of the pilot.

The general objective of this study is to review the relevance and effectiveness of age limitations for pilots involved in CAT Operations. For this, specific objectives are set as follows:

- Identify the most important age-related health risks for pilots that may lead to incapacitation in different types of aircraft CAT operations (Part 1);
- Gather health data representative of pilots' population in EU and for assessing main risk factors influenced by age (Part 1);

- Develop a comprehensive risk probabilistic model for incapacitation using the data collected (Part 2):
  - Differentiating between different categories of aircrafts;
  - Differentiating between single or multi-pilot operations;
- Describe the appropriate risk-mitigation measures other than age limits for the identified risks in all circumstances described above (Part 3);
- Propose a number of tests (psychological, physiological, medical, etc.) to support aeromedical decision on the applicant's fitness on an individual basis (Part 4);
- Identify main recommendations for implementing the project results and extending them (if needed) through additional data collection(s) (Part 4).

1. Part 1. Literature Review and Gathering of Available Data

The objective of Part 1 was to analyse whether pilots have an age-dependent risk of incapacitation due to medical reasons by means of collecting statistical data and analysing the morbidity and medical fitness of pilots within the EU, differentiated by the CAT category and age groups.
The approach included:

- Analysis of literature data on incapacitation and medical fitness of EU CAT Pilots: identification of the main age-related health risks leading to total pilot incapacitation in different types of aircraft CAT operation by means of collecting and studying the relevant scientific and grey literature;
- Obtaining and cleaning available data concerning
  - Pilot incapacitation and
  - Health-related data of CAT Pilots from European National Aviation Authorities (NAAs);
- Integrated epidemiological analysis of the retrieved incapacitation and health related data, linking the main risk factors for incapacitation to morbidity and unfitness within the European pilot population, differentiated by CAT category, character of operation (average duration, special circumstances/conditions), and age;
- Description of risk factors for sudden incapacitation, and their relation to age.

1.1 Analysis of the Literature

A computerized systematic search of the published scientific literature was performed, followed by a selection procedure based on a set of predetermined inclusion criteria. The quality of the studies was determined and results were analysed and summarized. In total, 17 articles were found eligible and relevant for this project. Of those studies, 12 reflected risk factors for incapacitation (medical fitness of pilots), and in 7 of those 17 articles, incapacitation-related data were presented.
Most, but not all, authors found that the rate of incapacitations increases with increasing age. The level of evidence for the increase of incapacitations with age is considered to be moderate. Fifty to seventy percent of the medical incapacitations cannot be prevented by setting an age limitation because incapacitations caused by problems such as acute gastroenteritis, laser strikes, headache, and ear/sinus conditions are not age-related. However, in the context of whether the regulatory age limitations can safely be extended beyond the age of 60, it is important to consider the medical conditions that bear an increased incapacitation risk and of which this risk increases with increasing age. The most frequently reported age-dependent medical conditions that may lead, to total incapacitation are caused by cardiovascular, neurological, or psychiatric conditions and include sudden death, coronary artery disease, cardiac arrhythmias, pulmonary embolism, stroke (cerebral ischemic infarction, cerebrovascular accident, cerebral haemorrhage), syncope, late-onset seizure(s), and acute psychosis.

1.2 Analysis of Collected Data of Incapacitation of EU CAT Pilots

Data of accidents and incidents involving flight crew incapacitation in commercial air transport were obtained via EASA from ECCAIRS (European Co-ordination Centre for Accident and Incident Reporting Systems). The initial data sample contained 501 occurrences. The resulting sample contained 257 occurrences of medical flight crew incapacitation events. The data sample contained information on the age of the incapacitated flight crew member for only 63 of the 257 occurrences. Of those 63, in 13 cases, the incapacitation was related to a myocardial event. In contrast to this finding, a sample of general aviation pilot incapacitation events (obtained through the NTSB aviation database) predominantly consisted of myocardial events. This is most likely a result of the fact that myocardial events often lead to full incapacitation and therefore, in the case of single pilot operations, are catastrophic and as a result will be investigated by the NTSB. In conclusion, the analysis of ECCAIRS and NTSB databases provides evidence for a likely increase of in-flight incapacitation risk with increasing age. Moreover, the analyses show that myocardial events were the most frequent causes of in-flight incapacitations with a high fatality risk.

1.3 Analysis of Collected Data of Aeromedical Fitness of EU CAT Pilots in Relation to Age

Available data of medical evaluations concerning CAT Pilots from European National Aviation Authorities (NAAs) was requested from 18 preselected countries. Six countries supplied eligible data of good quality. The data represented the total number of pilots screened, their age, CAT category, and the number of pilots per subgroup that was declared unfit. In addition, the medical diagnoses for the individual cases that were declared (temporary) unfit were supplied as well. The data of the six countries were pooled after which the Class 1 and Class 2 medical examinations were analysed. The association between age group, CAT class and unfitness was determined.

The results of the analyses coincide with the outcomes of the literature study on the most frequent reasons for (temporary) grounding of pilots, being cardiovascular, neurological, and psychological/psychiatric conditions. Among Class 1 pilots, the data showed that there is a clear effect of increasing age on the medical disqualification rate with a more than doubling in the 51-60 age group compared to the 41-50 age group, followed by a slight decrease of the disqualification rate in >60 age groups. This slight decrease might be due to a healthy worker effect caused by self-selection and medical screening leaving the more physically and mentally fit older pilots in the workforce.

The results of the analyses also show that the most frequent reason for the grounding of pilots is a cardiovascular condition (19% of all reasons for grounding). This finding is in agreement with Årva and Wagstaff (2004) and Evans et al. (2001), who also found this as the leading medical condition, while Evans and Radcliffe (2012), Høva et al. (2017), and Jordaan (2017) found similar percentages for cardiovascular conditions (14%, 18%, and 18% respectively). The results of the present study show a significant increase of unfitness cases due to cardiovascular conditions with increasing age, which is in agreement with the age-dependent increase in cardiovascular mortality and morbidity of commercial pilots described in other studies (Zeeb et al., 2003; Linnersjö et al., 2011).

We consider that the data analysed provides a fair representation of the European pilot population. However, the analysis of the NAA data has some inevitable limitations as well. First, a larger response rate of the NAAs would have led to a more robust dataset and results that were better generalizable. In addition, when interpreting the differences between ≥60 pilot cohorts and younger pilot cohorts one should take into account that there may be a selection bias due to a possible healthy worker effect occurring in the ≥60 cohort. Next, some medical conditions could have been assigned differently according to interpretation. On the other hand, an asset of the present analysis is that the collected NAA data included considerably more cases of Class 1 pilots aged 61-65 (n=1,843) and >65 years (n=763) than comparable studies (Høva et al., 2017; Evans & Radcliffe, 2012; Kagami et al., 2009; Årva & Wagstaff, 2004; Miura et al., 2002). In these studies the low number of commercial pilots over 60 years of age was mentioned as a limitation of the study.

1.4 Risk Factors for Sudden Incapacitation and Their Relation to Age
Section 5 (of Part 1) describes an analysis of the epidemiological literature on the effect of aging on medical conditions that have been found to bear a high risk to cause in-flight incapacitation (sudden death, cardiovascular conditions, stroke, syncope, seizures, migraine, acute psychosis, and nephrolithiasis). This analysis is based on the epidemiological data of the general population. It was taken into account that studies on pilot populations show that the standardized risk of pilots to die from cardiovascular or cerebrovascular diseases is significantly lower compared to the general population.

1.5 Discussion and Conclusion
In-flight incapacitation as a consequence of medical problems is a rare event occurring up to 0.45 times per 106 flight hours or 0.25% per annum. The literature study in this project provided moderate evidence that the incapacitation rate increases with age. This concurs with the outcome of the analysis of data of the ECCAIRS system on incapacitation of EU CAT Pilots, as well as with the data of the NTSB database. Fifty to seventy per cent of the medical incapacitations cannot be prevented by setting a regulatory age limit because incapacitations caused by problems such as acute gastroenteritis, laser strikes, headache, and ear/sinus conditions are not age-related. In the context of the question whether the regulatory age limitations for all CAT pilots can safely be extended, only the medical conditions that include an increased incapacitation risk with increasing age should be considered. The results of the present literature review, the analyses of the collected NAA data, and data of the ECCAIRS system in relation to age, indicate that it is appropriate to concentrate surveillance of pilots at greatest risk of cardiovascular and cerebrovascular medical events, especially those over the age of 50.
Although not in the context of the current research in which only total incapacitation was to be considered, it should be considered that inadequate pilot performance is a causal factor in 35-75% of accidents. Considerations concerning age limitations should therefore not solely be based on the medical fitness, but also on other aspects like individual cognitive and sensory performance in order to generate a more complete picture of the pilot’s ability to fly safely.

2. Part 2. Risk Assessment Based on Operations Considerations

In part 2 a probabilistic risk model for total sudden incapacitation using the outcomes from Part 1, is described. Flight crew incapacitation probabilities are estimated as a function of flight crew age and are compared with established risk acceptability thresholds. The estimates of flight crew incapacitation probabilities are based on age-dependent estimated mortality risk rates and hospital admission rates described in literature. The cardiovascular mortality rate was considered as the lower estimate of sudden complete incapacitation risk, whereas the rate of hospital admissions due to myocardial infarction and acute coronary syndrome was considered as the upper estimate.
The approach for determining risk levels and comparison with acceptability criteria is similar to the approach applied for aircraft system safety assessments as described in aircraft certification specifications (CS). This is essentially a risk based approach, providing requirements for a logical and acceptable inverse relationship between the probability and severity of a failure condition. The results of Part 1 are used to estimate the likelihood of sudden and complete pilot incapacitation as a function of pilot age. The likelihood is expressed as an average probability per flight hour. A sudden and complete incapacitation of a pilot in a multi-pilot operation is considered a major failure condition. A sudden and complete incapacitation of a pilot in single pilot operations is considered a catastrophic failure condition.

The study was limited by a lack of information on reported in-flight incapacitation events. The data in the European Central Repository for accident and incident reports in aviation are of poor quality; the cause of incapacitation, crew member involved and age of the incapacitated person are often not recorded.

For multi-pilot aircrew the lower and upper estimates of the probability of sudden complete age-related pilot incapacitation fall in the ‘extremely remote’ and ‘remote’ range of likelihoods, as defined by EASA CS 25 for aircraft system failures. Considering the effect of sudden and complete incapacitation of a pilot in a two pilot crew as a major condition, the associated probability of occurrence must be remote. The estimated incapacitation rate meets this requirement for all age groups up to and including the 75-84 age group. The upper estimate of the probability of sudden complete age-related pilot incapacitation crosses the 1% rule limit at the 55-65 age group. The upper estimate of the probability of sudden complete age-related pilot incapacitation crosses the 2% line, which corresponds with a probability of 2.28x10-6 per hour, around the age of 80. These results suggest that allowing pilots older than 65 in multi-pilot CAT operations would probably require additional risk-mitigation measures such as specific tests to support aeromedical decision on the applicant’s fitness on an individual basis.

For single pilot operations, sudden complete pilot incapacitation is a catastrophic event. The upper estimate of sudden complete incapacitation crosses the acceptability limit for catastrophic system failures for CS 23 aircraft with a single reciprocating engine and a seating capacity for 0-6 passengers at the 55-64 age group, while for multiple reciprocating engines or a single turbine engine it crosses at the 35-44 age group. The lower estimate of sudden complete incapacitation crosses the acceptability limit for catastrophic system failures for CS 23 aircraft failures for aircraft with multiple reciprocating engines or a single turbine engine and a seating capacity for 0-6 passengers around the age of 65, and crosses the acceptability limit for catastrophic system failures for aircraft with a seating capacity for 7-9 passengers at the 45-54 age group. This would mean that for the more complex categories of CS 23 aircraft, the estimated probability of sudden complete incapacitation for pilots older than 60 does not meet the probability requirements that are defined in CS 23 for aircraft system failures. The results suggest that any increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet current accident acceptability values. The results also suggest that for single pilots operations of complex aircraft the incapacitation risk is relatively high. Specific tests to support aeromedical decision on the applicant’s fitness on an individual basis for all age groups are perhaps needed to reduce the accident risk.

3. Part 3. Screening of Cardiovascular Risks in Asymptomatic Pilots

From Parts 1 and 2 it was concluded that there is a compelling need to reduce the medical incapacitation risk of single flying CAT pilots in the 55-64 age range and an increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet current operational accident acceptability values. The by far largest number of total incapacitations is attributed to cardiovascular diseases and it is therefore considered that prevention of cardiovascular events may offer the best opportunity to significantly reduce the in-flight medical incapacitation risk in older CAT aircrew members. In Part 3, therefore, the use of simple risk estimation tools is discussed, followed by enhanced cardiological risk determination methods to be used in the second stage of the stratified risk assessment. A flow-chart of the stratified cardiovascular risk assessment procedure is provided in Figure 1.

3.1 Risk Estimation Tools for Risk Assessment of Cardiovascular Disease (CVD) in European CAT Pilots

Validity, reliability, predictive capacities, potential limitations of the available cardiovascular risk assessment tools to be used in the initial and enhanced diagnostic stages of stratified risk assessment were evaluated based on analyses of relevant literature collected through an extensive Medline search strategy. Based on the results of the literature study and expert opinion a stratified cardiovascular risk assessment is recommended in which CVD risk estimation tools (i.e. risk calculators) are used for the initial stage of CVD risk assessment in European CAT pilots. Ideally, the risk estimation tool selected

- is based on a derivation cohort that is representative for the national health status or that is externally validated for the national cohort in question (e.g., for Germany use a German population derived risk calculation);
- uses the risk factors that are considered to be crucial;
- has been shown good discriminatory power; and
- predicts the risk for a relevant outcome (i.e. 5 or 10 year risk) and endpoint (i.e. fatal CVD, fatal + non-fatal CVD, stroke).

In the context of screening European CAT pilots a 'European cohort-derived' estimation tool with 'hard' events such as myocardial infarction, stroke, or death (non-fatal + fatal CVD) as standardized endpoints is recommended. For initial screening of European CAT pilots the PROCAM algorithm appears to be an appropriate risk score system for CVD because the endpoints concern all CVD events (fatal + non-fatal) and the algorithm can be adapted for use in many European countries, thereby estimating CVD risk of a derivation cohort that is representative for the nationality in question.
The recommendation that all aircrew, especially those over the age of 40 years, should be periodically screened for cardiovascular risk using a resting ECG and risk estimating calculators, is in accordance with a current EASA requirement (MED.B.010 article 4) that indicates that for CAT pilots estimation of serum lipids, including cholesterol should be assessed at the first examination after having reached the age of 40 (EASA, 2011). High sensitivity C reactive protein (hs-CRP) ≥2.0 mg/L and apolipoprotein B ≥130 mg/dL can be considered as risk-enhancing factors that are useful to be included in the overall estimated risk.

Systematic cardiovascular risk screening, including use of an appropriate risk score tool, will enable a reduction of in-flight incapacitation risk, which is in particular necessary when allowing an extension of the age limit for single flying CAT pilots to 65 years. The consequence of using an appropriate risk estimation tool is that in addition to the current aeromedical examination required by EASA, at least blood levels of LDL-cholesterol, HDL-cholesterol, and triglycerides (and preferably hs-CRP) are periodically required to assess the cardiovascular risk. In addition, it is also recommended to implement systematic cardiovascular risk screening, in order to give individual advice on prevention of CVD through lifestyle management.

3.2 Enhanced Screening Methods

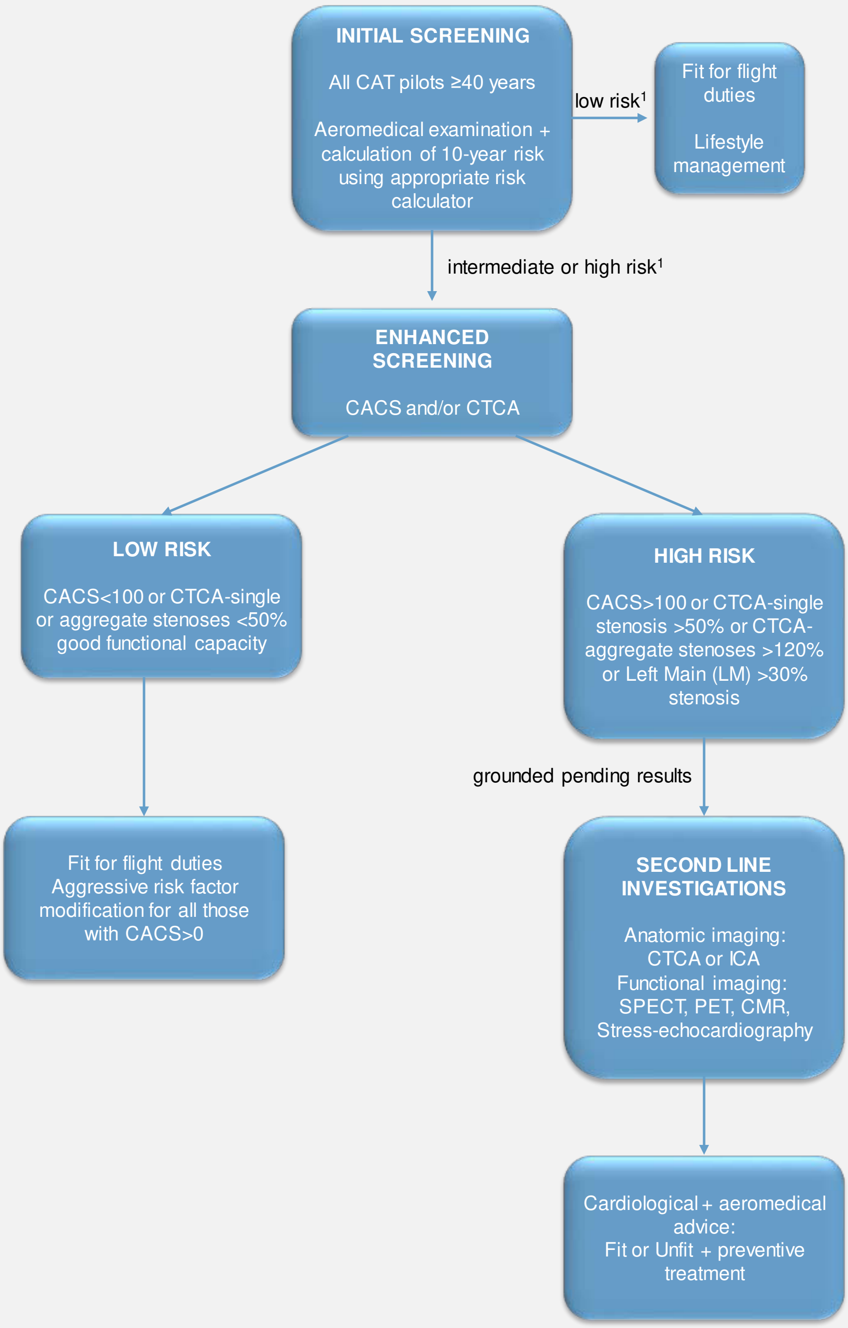
When the initial screening reveals an elevated or high CVD risk (e.g., >10% PROCAM risk score) or has a clinically determined higher risk of CVD, the pilot concerned should be referred to a cardiologist with aeromedical expertise for enhanced risk assessment in order to identify and substantiate the CVD risk and to advise on fitness for pilot duties and risk factor modification. Although the majority of cases of referral to cardiological expertise will concern coronary pathology (e.g., stenosis, plaques), it is emphasized that a cardiological examination is also indicated in cases of conduction abnormalities, arrhythmias, heart muscle disease, and valvular heart disease and aortopathy. An overview of generally accepted enhanced screening methods to assess the functional coronary capacity and identification of 'risky' plaques is given. For aircrew identified as being at increased risk for a coronary event based on the initial risk prediction, the use of one of the following generally accepted methods is recommended:

- CT Coronary Artery Calcium Score (CACS);
- CT coronary angiogram (CTCA);
- Vascular Ultrasound Imaging (VUI).

The use of CACS or CTCA allows to detect subclinical coronary atherosclerosis and thus, to identify asymptomatic individuals at increased risk for adverse coronary events. Both methods enhance the risk prediction compared with conventional risk factors.
CACS is a robust and reproducible way of detecting coronary atherosclerosis and to estimate future risk of cardiac events. A CACS >100 should result in aircrew being temporarily grounded pending further investigation of the individual cardiovascular risk using methods such as computed tomography coronary angiography (CTCA), myocardial perfusion scintigraphy (MPS), cardiovascular magnetic resonance imaging (CMR), and Invasive coronary angiography (ICA). CACS has the advantage over CTCA in that it is less expensive, is reproducible, and does not require intravenous contrast. However, CACS data provide no detail on extent and location of coronary stenosis on an individual basis and do not identify non-calcified coronary artery plaques. When available, and in the absence of contra-indications for I.V. contrast or β-blocker administration, it can be considered to use CTCA instead of CACS as a first step of enhanced cardiological screening. The specificity of CTCA decreases significantly with increased calcification and if CACS is greater than 1,000, CTCA is not recommended
Vascular ultrasound imaging and Carotid Intima-Media Thickness (IMT) can provide additive independent risk information in individuals at increased risk, but it should be considered that the predictive power of carotid IMT for cardiovascular events is weak and - in agreement with the ACC/AHA as well as ESC guidelines - it is recommended not to use these techniques to get additional information when screening asymptomatic aircrew.

3.3 Conclusion and Recommendations

The recommended procedure described above is depicted in Figure 1. For pilots of whom the initial risk is estimated to be between 5% and 10%, thorough lifestyle counselling is recommended, with an emphasis on preventive diet and exercise measures. Aircrew with a CACS >100 or CTCA-single stenosis >50%, CTCA-aggregate stenoses >120%, or Left Main (LM) >30% stenosis should be grounded pending further investigation of the individual cardiovascular risk. It is recommended that individuals with an initial risk score of >10% and a very low or zero CACS should undergo a CTCA examination in order to exclude the presence of coronary artery disease and risky non-calcified plaques. Use of IMT for additional cardiovascular evaluation is not recommended. Pilots in a low cardiovascular risk category (<10 %), and/or with a CAC score <100, are considered fit to fly, while it should be considered to give them lifestyle management advice in order to keep their CVD risk low. Stratified risk assessment should be periodically repeated (periodicity dependent of the age).



[1] The classification of a low, intermediate or high risk is given by the cardiovascular score being used. We recommend using the PROCAM score; in this case a 10-year cardiovascular risk of <10% is low, of 10-20% intermediate and of >20% high.

Figure 1 Flow chart with algorithm adapted from Gray et al. (2019). This algorithm is aimed at supporting AMEs and Medical Assessors. The second line investigations are in the realm of the consulted cardiologist

4. Part 4. Conclusions and Recommendations

The aim of Part 4 is to make concluding recommendations regarding the acceptable age limits for 1) CAT pilots flying single-piloted aircraft; and 2) CAT pilots flying multi-pilot operations, in order to keep the total in-flight incapacitation risk at an acceptable safety level. In addition, a set of methods is proposed to enhance identification of pilots at risk, to reduce the risk of total incapacitation, and to decide on the applicant's fitness on an individual basis. Moreover, the implementation of the proposed changes in aeromedical assessments are discussed, knowledge gaps are identified and priorities for future research and data gathering are addressed.

4.1 Age-Dependent Medical Risks Associated with Total Incapacitation

Although cardiovascular conditions are considered as the principal risk factor for total incapacitation, syncope, late-onset seizure(s), and acute psychosis are also possible age-dependent causes of sudden incapacitation. The risk of incapacitation due to these conditions should therefore also be reduced as much as possible. Therefore, the risk assessment of syncope, late-onset seizure(s), and acute psychosis is discussed, and possibilities for prevention are presented. Next, the reduction of incapacitation risk associated with age-dependent changes in the sensory system is addressed as well. The consequences and considerations regarding neurophysiological assessments and cognitive functioning are also described. Finally, the effects of long and irregular working hours, and overtime work on both cardiovascular risks and fatigue are discussed.

4.2 Conclusions and Recommendations for Preventive Measures and Age Limitations

4.2.1 Prevention: screen all aircrew over the age of 40

Early prevention of cardiovascular disease is considered to reduce the number of pilots at risk for incapacitation. As mentioned in the report of Part 3 and in accordance with ICAO recommendations on prevention (Jordaan, 2017), it is recommended to periodically screen all aircrew over the age of 40 on cardiovascular risk using a resting ECG and risk estimators ('calculators') that are representative and appropriate for the population to screen and include family history and provide non-fatal and fatal end points. When the risk score is ≥10%, enhanced screening methods should be used to further evaluate the individual CVD risk, possible preventive measures, and fitness to fly (see flow chart of Figure 1). For pilots of whom the initial risk is estimated to be between 5% and 10% (borderline risk), pro-active lifestyle counselling is recommended, with an emphasis on preventive diet and exercise measures.

4.2.2 Age limit single-pilot operations

Based on the outcome of Parts 1 and 2 it was concluded that the risk of the 55-64 age group is just within the margin of the acceptability limit for catastrophic system failures for single piloted CS 23 aircraft with a single reciprocating engine and a seating capacity for 0-6 passengers; and therefore, that there is a compelling need to reduce the medical incapacitation risk of single flying CAT pilots in the 55-64 age range. Any increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet current operational accident acceptability values. It is therefore recommended to extend the age limit of CAT pilots flying single pilot operations from 60 years to the pilot's 65th birthday, providing that additional measures are taken (see Table 1). A medical screening should be done every six months, as is currently required for single flying CAT pilots from the age of 40 onwards (MED.A.045). As an additional operational/functional requirement to the specific medical procedures, the pilot should be required to successfully pass a proficiency check or a simulator check (Licence Proficiency Check - LPC or an Operator Proficiency Check - OPC) every 6 months from age 60 to age 65. This is in agreement with the assumption that six-monthly simulator checks are better than a medical or psychological exam at checking cognitive performance and detecting pilots who fall below required standards, particularly if combined with line checks and peer review (Evans, 2011).

4.2.3 Age limit multi-pilot operations

Based on the outcome of Parts 1 and 2, it was concluded that allowing pilots older than 65 years in multi-pilot CAT operations would require additional risk-mitigation measures such as specific tests to support the aeromedical decision on the applicant's fitness on an individual basis. We recommend keeping the age limit at 65 years as it is currently set by EASA (FCL.065; EASA, 2016). The general medical examinations as well as the additional examinations and periodicity for multi-crew pilots between 60 and 65 years of age are also shown in Table 1.

Table 1 Recommended general medical examinations for Class 1 CAT pilots aged 60-65 with single and multi-pilot operations

Timing of routine examination	Complete general aeromedical examination	12-lead ECG	Blood lipids & blood sugar	Cardiovascular risk estimation	Specialist ophthalmological examination	Audiometry	Spirometry	LPC or OPC
Age								
60	✓	✓	✓	✓	✓	✓	✓	✓
60.5	✓							✓
61	✓	✓	✓	✓				✓
61.5	✓							✓
62	✓	✓	✓	✓	✓	✓		✓
62.5	✓							✓
63	✓	✓	✓	✓				✓
63.5	✓							✓
64	✓	✓	✓	✓	✓	✓		✓
64.5	✓							✓
65	Class 1 medical certificate expires							

A comprehensive risk assessment should include a full clinical history and physical examination of which the contents are laid down in EASA Part-MED.A.010 (EASA, 2019) and the Acceptable Means of Compliance and Guidance Material. This general aeromedical examination should cover all factors associated with incapacitation risk. Apart from the possible medical complaints, the AME needs to question about a variety of issues in order to identify 'red flags' concerning physical or mental health risks. These issues concern the applicant's job (type of flying, satisfaction, workload, etc.), commuting (home-work), financial worries, sleep, medication, drugs/alcohol/smoking habits, exercise and diet, family arrangements, security, hobbies, and holidays. Information should be gathered to be used for calculation of a risk score and other modifiable and non-modifiable risk factors to be considered in making a clinical judgement about the individual's total CVD risk. Smoking status, blood pressure, serum lipids, waist circumference and BMI, nutrition, physical activity level, and alcohol intake are considered as modifiable risk factors, while age, gender, family history of premature CVD, and social history are considered as non-modifiable risk factors. Related conditions that could contribute to CVD risk, such as diabetes, chronic kidney disease, familial hypercholesterolemia, and the presence of atrial fibrillation (AF) should also be considered. In addition, the use of the following methods is described in the report of Part 4:

- 12-lead resting ECG;
- blood lipids and blood glucose;
- cardiovascular risk estimation;
- specialist ophthalmological examination;
- audiometry;
- spirometry;
- additional neurological examinations.

4.3 Considerations and Future Directions

4.3.1 Availability of Medical Screening Data of National Authorities

In the present project it was found that the majority of the European National Aviation Authorities (NAAs) were unable to provide their medical evaluations data concerning CAT pilots. Reasons given were inaccessibility of the data and inability to retrieve the data. Therefore, it was recommended to improve the system in order to enable a sound evaluation of medical screening results from CAT pilots.

a) National authorities should be enabled to register all data concerning medical evaluations of CAT pilots in an easily accessible format in order to assess trends in age-dependent medical conditions and to evaluate the effects of medical flight crew licensing requirements. An inventory should be made of existing systems and/or methods, with special reference to accessibility and user-friendliness. Proper accessibility of the NAA databases is a prerequisite for the evaluation of the effectiveness of the cardiovascular and other risk assessment procedures. Such evaluation is essential for future considerations concerning raising or abolishing age limits for CAT pilots.

b) Because it is foreseen that developments to improve the accessibility of the NAA databases as mentioned above under a) are likely to take time, it is recommended to start already with a follow-up study aimed at assessing the risk factors and incidence of incapacitating events. For this study, pilots who are currently aged 63-65 years should be monitored during a predefined number of years, also covering the post-retirement period.

c) Because the systematic cardiovascular risk assessment as recommended in the present report should be evaluated on efficacy and cost-effectiveness, national authorities should collect the data of all individual scores of the cardiovascular risk calculation (done in the initial screening), the consequences of the score, as well as the outcome of enhanced screening.

4.3.2 Follow-up system Pilot's Health

In most Member States it is impossible to do a complete evaluation of the accuracy of the medical decisions taken by the NA, AeMC, AME. This is due to the very limited possibilities for medical follow-up of pilots who have stopped flying due to health problems without informing the NA or AeMC, death and cause of death of retired pilots. It is expected that such follow-up might be hindered by national legislation (privacy, etc.). In a research project an inventory of opportunities, limitations and methods to collect these data should be made.

4.3.3 Optimize registration of in-flight incapacitation occurrences

In the present project it was concluded that the usefulness of the ECCAIRS database to identify medical and age-dependent causes of in-flight incapacitation was very limited. In many cases information on age, (medical) cause, and operational consequences was lacking. Therefore, general population data were used to make risk estimations. It is recommended to improve the system in order to enable a sound evaluation of medical in-flight incapacitation risks.

4.3.4 Sensitivity and validity of dedicated simulator checks and neuropsychological assessment

In addition to evaluation of medical risk assessment procedures, research and developments should concern development of sufficiently sensitive and valid dedicated simulator checks and/or cognitive tests in order to consider further extension of the upper age limits for CAT pilots.

Some national authorities who already allow single flying CAT pilots to continue flying until 65 years of age mandate an ‘extended psychological test including cognitive skills’, or ‘psychological testing’, or ‘assessment of cognitive abilities’. Although it is understandable that such tests might ease one’s feeling of safety, this is currently not recommended in the present report. Currently, it is assumed that simulator checks, line checks, and peer review provide the best opportunities to detect below standard performance. The recommended research should be aimed at incorporating assessment of essential cognitive factors of flight performance in the regular mandatory License Proficiency Checks (LPC) or Operator Proficiency Checks (OPC). Attention should be focused on abilities to function under highly stressful demands, such as high time pressure. In that context, it is recommended to develop a framework for assessing and scoring cognitive performance based on results of the proficiency checks.

Content

Part 1 Literature Review and Gathering of Available Data (Deliverable No. 1)

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Content

1 Introduction

1.1 Total incapacitation risk in commercial air transport and risk by age

Articles that address medical causes and prevalence of in-flight incapacitation and impairment generally support the idea that this is correlated with age. However, studies attempting to derive the rate of incapacitations caused by medical conditions and/or an incapacitation rate as a dependent variable which is affected by age are scarce. Huster et al. (2014) found an in-flight incapacitation rate of 0.19-0.45 per 10^6 flight hours and an age-depending increase in incapacitation in a systematic review of 10 studies covering study periods of 1945 up to 2004. A problem to interpret the results of this review is the fact that the included data are all collected before 2004. The results might therefore not completely reflect the current public health level, considering that at present the overall risk of death and of acute medical incapacitation for a person with the age of 60 to 69 years is considerably lower than before the year 2005 (WHO, 2016; Eurostat, 2018). In addition, it is difficult to define an unequivocal relationship between incapacitation and age because, as age progresses, large individual differences in physical and mental aspects exist and group averages are poor predictors of individual health and performance. Many medical conditions potentially leading to in-flight incapacitation are not strictly related to age. While cardio- and cerebrovascular conditions tend to occur more in older people, other medical conditions, such gastro-intestinal conditions, might occur at younger or random ages. Moreover, medical conditions that have the potential to result in an incapacitation, might not lead to an actual operational incapacitation; e.g., a myocardial infarction has a high potential to result in incapacitation, but during a “silent” myocardial infarction a pilot might not experience incapacitating symptoms. Further, it is inevitable, that it might be difficult to prove that an accident - especially with fatal outcome - was a consequence of an incapacitation. Most studies have analysed operations with at least two pilots in which the incapacitation could be witnessed by the colleague pilot. In single-pilot operations however, a total sudden incapacitation may more often lead to a fatal accident. The number of incapacitations in single-pilot flights might therefore be under- or overestimated as no witness can tell what happened and often autopsy and medical history only provide a probable cause.

Evaluating literature on medical incapacitations and its relation to age is also hindered by the fact that a comparison of the results of studies is complicated by inconsistency in the denominator, e.g., ‘10^6 flight hours’, ‘number of pilots studied’, ‘year’, ‘fatal accidents’ and non-uniformity of the definition of incapacitation: it might be ‘any change in ability to function appropriately’, ‘a medical event that resulted, or would have had the propensity to result, in an inability to act as flight crew for at least 10 min’ (Evans & Radcliffe, 2012), or a partial incapacitation associated with symptoms that (would have) resulted in a reduction of function or distraction from the flight crew task. Moreover, it might be only in-flight or both in- and off-duty, it can be any incapacitation or only (e.g.) cardiac incapacitation, and it might be caused by either a disease or by external causes (e.g., laser strike, fumes, hypoxia). In this context it was decided to use ‘an inability to function appropriately as flight crew’ as work definition of total incapacitation in the present study.

Finally, when the focus is on the incapacitation risk of 60+ pilots, comparisons with younger pilot cohorts are difficult to interpret due to the limited number of active pilots beyond the age of 60. This is even more true concerning 60+ pilots engaged in commercial single-pilot operations, due to the very existence of the Age 60 Rule, which prohibits commercial single-pilot operations for pilots aged 60 and over in most countries, and due to the fact that most commercial single-pilot operations are operated by small companies employing only a few pilots.

1.2 Medical causes of in-flight incapacitation

As mentioned above, evaluating the medical causes of incapacitation is hindered by the fact that a comparison of the results is complicated by differences in the definitions of incapacitation denominator (e.g., per 1,000 pilot-years, number of pilots) and possible differences in diagnostic criteria that were applied: e.g., syncope can be categorized as 'cardiovascular', or 'neurological', or 'loss of consciousness.' The main medical reasons (50-70%) for in-flight incapacitation of active pilots seem not to be age-related (i.e. acute gastroenteritis, laser strikes, toxic smoke and fumes, ear/sinus conditions, headache (James & Green 1991; ICAO, 2012; ATSB, 2016)). In their recent report the Australian Transport Safety Board found that in high capacity operations (>38 seats) gastro-intestinal illness accounted for 54% of the incapacitations, laser strikes for 13%, while 5% concerned loss of consciousness (cause not specified) (ATSB, 2016).
Table 1.1 shows the results of a survey that ICAO sent to its Member States in 2016 requesting information on causes for medical incapacitation of professional pilots (Jordaan, 2017). It should be mentioned that in this global survey diagnostic criteria may vary between different parts of the world. Moreover, demographic and epidemiological disease patterns may also cause large differences. This ICAO survey mentions 'mental health' to cause 16% of the incapacitations. However, it is not clear whether mental health includes psychological and psychiatric problems, or just one of the two diagnostic categories.

Table 1.1 Incapacitation of professional pilots by medical condition (results of ICAO survey 2016; Jordaan, 2017)

Medical Category	Frequency (only occurrences >4% are shown)
Mental Health	16%
Cardiovascular	14%
Metabolic	9%
Gastro-intestinal	6%
Respiratory	6%
Vision	5%
Otorhinolaryngological (ENT)	4%
Neurological	4%
"General ailment"	4%

Although prevention of the non-age-dependent causes of in-flight incapacitation is warranted, medical causes of sudden incapacitation that could be age-dependent should be the focus when considering a possible extension of the age limit of pilots.

1.3 Objectives

The objective of this task is to analyse whether pilots have an age-dependent risk of incapacitation due to medical reasons by means of collecting statistical data and analysing the morbidity and medical fitness of pilots within the EU, differentiated by the CAT category and age groups.
The approach for this task includes:

1. Analysis of literature data on incapacitation and medical fitness of EU CAT Pilots: identification of the main age-related health risks leading to total pilot incapacitation in different types of aircraft CAT operation by means of collecting and studying the relevant scientific and grey literature;
2. Obtaining and cleaning available data concerning
    a. Pilot incapacitation and

b. Health-related data of CAT Pilots from European National Aviation Authorities (NAAs);

3. Integrated epidemiological analysis of the retrieved incapacitation and health related data, linking the main risk factors for incapacitation to morbidity and unfitness within the European pilot population, differentiated by CAT category, character of operation (average duration, special circumstances/conditions), and age.

2 Analysis of Literature Data on Incapacitation and Medical Fitness of EU CAT Pilots

2.1 Method

A computerized systematic search of the published scientific literature was performed, based on an extensive list of searchable keywords and areas of interest. The corresponding search strategy was drawn up in close collaboration with an Information Scientist (first #1 and #2 were combined, after which #3 and #4 were added).

1. Flight Crew/airline pilot(s)/co-pilot(s)/naval pilot(s)/pilots of airlines/airline pilots/helicopter pilots/airline crew/airplane pilot(s)/test pilots/fighter pilots/aircraft pilots/commercial pilots/HEMS pilots/ambulance pilots/police pilots
2. Age limit/effect of aging-ageing/aging-ageing/older/aged
3. Medical/medication/Physiology/neuro-psychological/cognitive function(s)/operational functioning/functional capacities/aeromedical fitness/medical fitness/sensory system/sensorial/ophthalmological/auditory/orientation/vestibular/auditory assessment/ophthalmological/mental health/cardiovascular/neurological/mental health/in-flight incapacitation/pilot incapacitation/incapacitation
4. Publication date: from 1996 onwards

Only literature published from 1996 onwards was selected because
1. The process of harmonizing aeromedical rules was started in Europe that year, resulting in implementation of JAR-FCL1 (14 February 1997); and
2. It was assumed that results of older studies do not reflect the largely improved European public health, mortality, and morbidity levels (WHO, 2016; Eurostat, 2018).

The search strategy was applied into the databases of Scopus, the Cochrane library and PsycINFO. Based on the expert knowledge and existing network of the research group, relevant ‘grey’ literature (i.e. publicly available reports of national and international institutes and authorities, legal reports) was retrieved as well.

The search was followed by a selection procedure based on a set of predetermined inclusion criteria:
- Language and literature: Peer-reviewed and written in English or Dutch;
- Design: Cross-sectional, case-control, prospective of retrospective;
- Population: Helicopter, CAT, general, or military pilots;
- Outcome: A form of total incapacitation, or a risk factor for total incapacitation;
- Analyses: The collected data is used to describe the association between age and (total) incapacitation.

Next, the retrieved abstracts were checked by two reviewers independently. Full texts of the articles were acquired if they met all inclusion criteria, and consensus was met by the reviewers about possible disagreements. In the second phase, the selected publications were studied in more detail. Snowball sampling (checking of the citations) was applied, after which a final selection was made. Next, the quality of the studies was determined and results were analysed and summarized. The quality was determined by means of a modified version of the checklist used by Merkus et al. (2012) and consisted of 12 items concerning the objective, population, exposure assessment, outcome assessment, confounding assessment, and analysis and data presentation of the study (Table 2.1). A study was considered to be of high quality if it scored positive on more than 50% of the applicable items.

Table 2.1 Quality assessment checklist. CS = cross-sectional, CC= case-control, PRC=prospective or retrospective cohort study

Topic	#	Item	Type of study
Study objective	1	Positive if a specific, clearly stated objective is described	CS, CC, PRC
Study population	2	Positive if the main features of the study population are described (sampling frame and distribution of the population by age and sex)	CS, CC, PRC
	3	Positive if the participation rate is ≥80% or or if it is lower, the nonresponse is not selective (data presented)	CS, CC, PRC
Exposure assessment	4	Positive if data are collected and presented about occupational exposure in the past and during the follow-up period.	CS, CC, PRC
Outcome assessment	5	Positive if the outcome measure is measured the same for all participants using a standardized method.	CS, CC, PRC
	6	Positive if data were collected for -1 year.	CS, CC, PRC
Confounding assessment	7	Positive if the most important confounders (age, health status, gender) are measured and used in the analysis	CS, CC, PRC
	8	Positive if confounders are measured the same for all participants using standardised methods of acceptable quality	CS, CC, PRC
Analysis and data presentation	9	Positive if the appropriate statistical model is used to evaluate the data	CS, CC, PRC
	11	Positive if measures of association are presented (OR/RR), including 95% CIs and numbers in the analysis (totals)	CS, CC, PRC
	12	Positive if the number of cases in the multivariate analysis is at least 10 times the number of independent variables in the analysis	CS, CC, PRC

To be able to draw up conclusions about the main risk factors for incapacitation, a level of evidence synthesis was used. This synthesis takes into account the methodological quality and the results of the selected studies and makes a distinction between strong (consistent findings in multiple high quality studies), moderate (consistent findings in one high-quality study and in one or more low-quality studies), and insufficient (only one study available or inconsistent findings in multiple cohort studies) evidence.

2.2 Results

The search strategy resulted in 440 potentially relevant articles. After the selection procedure based on the title and abstracts only, 401 articles were excluded, and 49 full texts were acquired. In the second step, 17 articles were found eligible and relevant for this project. Of those studies, 12 reflected risk factors for incapacitation (medical fitness of pilots), and in 7 of those 17 articles, incapacitation-related data were presented.

2.2.1 Quality

The subsequent quality assessment of the included peer reviewed articles resulted in 7 studies that were regarded as being ‘high quality’ and 10 studies as being of ‘low quality’ (Table 2.2). Since they were not peer-reviewed, the reports originating from the grey literature were all regarded as being of low quality.

Table 2.2 Results of the quality assessment

Study	Description	Quality score
Årva & Wagstaff (2004)	Reasons for medical disqualification among Norwegian CAT pilots	Low
Evans & Radcliffe (2012)	Incapacitation rate + diagnoses unfitness UK CAT pilots	High
Kagami (2009)	Diagnosis unfitness Japanese commercial pilots	Low
Linnersjö (2011)	Mortality and acute myocardial infarction incidence among Swedish commercial and military pilots	High
Mitchell & Evans (2004)	Quantitative incapacitation risk assessment concerning medical fitness of multicrew CAT pilots	High
Miura (2002)	Health and incapacitation risk 60-63 yr Japanese CAT pilots	Low
Qiang (2003)	Mortality of US Commuter-Taxi pilots	High
Sykes (2012)	Health data Oceanic CAT pilots	High
Zeeb (2003)	Cardiovascular mortality of German CAT pilots	High
Newman (2007) (grey)	Medical conditions of pilots involved in accidents and incidents from 1975 to 2006 - ATSB report - not peer reviewed	Low
ATSB (2016) (grey)	Medical reasons of sudden incapacitation of active pilots from 2010-2014 - ATSB report - not peer reviewed	Low
Simons et al. (1996) (grey)	Accident rates; Risks of medical and cognitive incapacitation + recommendation to control risk in case of raising the CAT age limit to 65 - Report not peer reviewed	Low
Evans (2001) (snowball sampling)	Incapacitation rate + diagnoses unfitness UK CAT pilots (not peer reviewed congress presentation)	Low
DeJohn et al. (2004) (snowball sampling)	Incapacitation rate - CAMI/FAA report- not peer reviewed	Low
Müller et al. (2014) (snowball sampling)	retrospective observational study of incidents during HEMS operations	High
Høva et al., (2017) (snowball sampling)	Reasons for medical disqualification among Norwegian CAT pilots	Low
Jordaan (2017) (snowball sampling)	Medical reasons incapacitation - not peer reviewed congress presentation	Low

2.2.2 Outcomes: incapacitation or accident rates in relation to age

Table 2.3 shows the outcomes of the literature review concerning accident rates, incapacitation rates and the relation to age.

Table 2.3 Outcome of the included studies: accidents, incapacitation rates and relation to age

Study	Data collection period	Population	Reporting metric	Accident or Incapacitation Rates
Simons et al., 1996	1993	FAA Class I (airline), II (commuter-taxi), and III (private) pilots	Review of Retrospective study of number of accidents in FAR Part 121 (air carrier), Part 135 (commuter/air taxi) & Part 91 (general aviation) operations.	• Class I ≤60 yr: no evidence for increase of accident rate with increasing age • Class II & III≤69 yr: no evidence for increase of accident rate with increasing age • Major determinants of accident rate=total flight hours and recent flight hours
Miura, 2002	1991-2000	Japanese ATPL pilots including pilots >60 with additional medical testing	Number of accidents and pilot's health status	<60: 323 accidents/10 yrs 60–63: 0 accidents/10 yrs 20 of 159 pilots >60 failed medical test/retired
DeJohn et al., 2004	1993-1998	All FAA licensed US Airline pilots	Retrospective study: In-flight incapacitation rate (and impairment rate)	• Incapacitation rate: 0.45 per 10^6 flying hours • Impairment rate: 0.13 per 10^6 flying hours • Increase with age - no data of pilots ≥60 yrs
Mitchell & Evans, 2004	2000	UK CAT licence holders	Prospective study: Estimated in-flight deaths due to cardiovascular reasons based on 127 incapacitations in 10,500 aircrew over 10 yr	• Estimated number of • deadly cardiovascular • in-flight incapacitations • in 10 yrs: 6 (observed actual number: 2 in 10 yrs). • Increase with age.
Newman, 2007	1975-2006	All Australian CAT and private pilots involved in accidents and incidents	ATSB data: Number of accidents and incidents caused by a medical condition	• 98 occurrences of medical incapacitation (0.19% of all accident/incidents). In 10 of 98 cases outcome was fatal (all single-pilot operations) • Relation with age not analysed
Evans & Radcliffe, 2012	2004	All (16,145) UK/JAR Class I licence holders	Retrospective study: Real data of in- and off-flight incapacitation due to medical reasons	Total annual incapacitation rate: 0.25 % - increasing with age: 20-29: 0,11% 30-39: 0,12% 40-49: 0,23% 50-59: 0,42% 60-69: 1,20%

Study	Data collection period	Population	Reporting metric	Accident or Incapacitation Rates
Müller et al., 2014	2007-2011	257 Austrian and German HEMS pilots	Retrospective observational study of incidents (liability damages) during HEMs ops	Mean number liability damages: ≤35 yr: 0.95-1.77 ≥60 yr: 0.25-1.53 No effect of age
ATSB, 2016	2010-2014	All Australian CAT + private pilots	ATSB data: Number of incapacitations	Total 113 incapacitations. • High capacity OPS (≥39 seats or >4,200 kg payload): 86 (1 per 34,000 flights). • Low capacity OPS (<10 pax or jet A/C <3,500 kg): 12 • General aviation (most single pilot): 15 • Relation with age not analysed

As can be seen, one study assessing the accident rate found no significant increase of accident rate with increasing age and found that the accident rate for all age groups decreased as the number of total flight hours and recent flight hours increased (Simons et al., 1996). Miura (2002) studied the accident rate of Japanese CAT pilots, who are allowed to continue flying up to the age of 63 and found no accidents of these pilots during 10 years. It should, however, be considered that accident rate is a surrogate marker for in-flight incapacitations, and that not every accident is caused by medical incapacitation and that not every incapacitation will lead to an accident. The same applies to the findings of Müller et al. (2014) who assessed the number of liability damages of Austrian and German HEMS pilots. They found no significant effect of age, but it should be considered that 1) liability damages are a rather remote surrogate for incapacitations, that 2) the mean number of participating HEMS pilots ≥60 was only 12.8 during the years of study, and 3) that a healthy worker effect might have influenced the outcome.

The other studies that assessed in-flight incapacitation rates found an increase of incapacitation risk with increasing age (DeJohn et al., 2004; Mitchell & Evans, 2004; Evans & Radcliffe, 2012). The level of evidence is considered as moderate (consistent findings in one high-quality study and in one or more low-quality studies). A limitation of the studies that reported an age dependency of incapacitations is that these studies are based on data collected before 2005 and, therefore, the results might not completely reflect the current public health level. Reaching the age of 60, a citizen of the European Economic Area had a life expectancy of 15.4 years in 2005 and of 18.6 years in 2016 (Eurostat, 2018). Based on these demographic statistics, it is likely that the present overall mortality rate and morbidity rate - and thus possibly the incapacitation rate - for a person aged between 60 and 69 is lower than before 2005.

2.2.3 Outcomes: reported medical causes of total incapacitation

Table 2.4 shows the outcomes of the literature review concerning medical causes of total incapacitation. It can be seen that in the majority of the cases incapacitations are caused by conditions that cannot be prevented by setting an age limit, such as gastro-intestinal conditions, laser strikes, and toxic fumes. This is in agreement with the results of studies done in the 1980s (James & Green, 1991). In most of these cases the literature is not clear about the operational consequences of these conditions (total incapacitation, impaired performance, or non-impairing uncomfortable symptoms).

Although not quantified, DeJohn et al. (2004) mention that cardiovascular (myocardial infarctions and cardiac arrhythmias), neurological (epileptic seizures), and gastro-intestinal symptoms were the most frequent causes of medical incapacitation in the 55-59 age group, which was the highest age group that could be studied. Evans et al. (2001) provided a detailed report of 127 incapacitation events, of which 20 were considered 'serious' resulting in total incapacitation manifested by loss of consciousness or inability to contribute to the flight operation for a prolonged period. The causes of these serious incapacitations concerned 2 cardiac, 4 neurological, and 6 gastro-intestinal conditions, while the cause was unknown in 8 cases. Evans and Radcliffe (2012) also gave a detailed analysis of total off- and in-flight incapacitations. In their study of all UK CAT license holders in 2004, they found that cardiovascular and cerebrovascular conditions led to 50% of the 36 incapacitations and 2 of the 4 sudden deaths. The cardiovascular cases included 8 cases of acute myocardial infarction (6 cases) or chest pain (2 cases) with an age range of 39-64 years, 3 cases of arrhythmia (age range 42-66 yrs), and 2 cases of pulmonary embolus (ages 45 and 49 yrs). The cerebrovascular cases concerned 4 strokes (age range 33-59 yrs) and one subarachnoid haemorrhage (48 yrs). Other cases occurring more than one time concerned panic attack (3), spontaneous pneumothorax (4 cases), and epilepsy (2 cases). Newman's analysis of the Australian Transport Safety Bureau's database revealed 98 in-flight medical incapacitations (Newman, 2007). There were a total of nine cardiovascular cases (9.2%) that occurred in-flight of which eight cases where described as a heart attack (8.2%). Of these, five cases in single-pilot operations resulted in a fatal accident. The reasons for the loss of consciousness were not specified, therefore it is not possible to attribute this to cardiovascular, neurological, or vasovagal causes.
It is concluded that the most frequent and possibly age-dependent medical causes of a serious and total incapacitation are cardiovascular, cerebrovascular, and neurological conditions.

Table 2.4 Most frequent reported medical causes of total incapacitation

Reference	Report based on:	Medical cause	Frequency (% or #)
Evans (2001)	Review of the UK CAA's Mandatory Occurrence Report (MOR) database for the period 1990-1999	127 incapacitations:	54% GI 3% neuro 2.5% CV 20% possible CV
		20 serious **total** incapacitations:	#6 GI #4 neuro # 2 CV # 8 unknown
DeJohn et al. (2004)	In-flight medical incapacitation and impairment of U.S. CAT pilots 1993 to 1998	most frequent causes of incapacitation in the 55-59 age group	CV, Neuro, GI not quantified
Newman (2007)	ATSB database of medical conditions of pilots involved in accidents and incidents from 1975 to 2006	98 incapacitations 10.2 % fatal (all single-pilot ops)	21% GI 12% toxic fumes 9% LOC (not spec.) 8.2% CV (5 cases fatal)
Evans & Radcliffe (2012)	Analysis of in- and off-flight incapacitations of all UK CAT license holders	36 Incapacitations	31% CV 19% neuro 5.5% pulmonary embolus 11% spontaneous pneumothorax 8.3% panic attack
		16 in-flight 'problems' Reported to CAA	69% psychiatric

Reference	Report based on:	Medical cause	Frequency (% or #)
ATSB (2016)	All in-flight incapacitations in ATSB database between 2010-2014	Total 113 incapacitations In high capacity + low capacity + general aviation operations	42% GI 17% Laser strikes 7% LOC (not spec.) 6% multiple symptoms 3% eye condition 2% heart attack Rest various causes

GI=gastro-intestinal, Neuro=neurological, CV=cardiovascular, LOC=loss of consciousness, ATSB=Australian Transport Safety Bureau.

2.2.4 Outcomes: reasons for aeromedical disqualification

Disqualification or (temporary) grounding of pilots for medical reasons is based on the consideration that the medical condition concerned bears an unacceptable risk of in-flight incapacitation. In the context of the present study, medical conditions related to a loss of license, or (temporary) grounding can therefore be used as indicators of potential incapacitation. Based on the results of the literature review, table 2.5 shows the most important reasons for (temporary) grounding of pilots.

Table 2.5 Description of the included studies most frequently reported (>5%) reasons for grounding of pilots and relation to age

Reference	Cohort/Data (study period)	Report based on:	Diagnostic category- frequency	
Årva & Wagstaff (2004)	Norwegian commercial pilots - 48,229 pilot-years (1982-2001)	Medical reasons for grounding of 275 CAT pilots rate 5.7/1,000 pilot-years.	Cardiovascular Neurology Musculoskeletal Psychiatry ENT	35% 15% 13% 13% 8%
Evans (2001)	UK professional pilots (2001)	Medical reasons for grounding of 61 UK CAT pilots	Cardiovascular Neurology Psychiatry Diabetes ENT	36% 18% 8% 7% 7%
Evans & Radcliffe (2012)	16,145 Class 1 UK commercial pilots (2004)	Analysis of reasons of (temporary) unfitness of 720 pilots	Accidents Musculoskeletal Cardiovascular Psychiatric Gastrointestinal	18% 18% 14% 10% 8%
Høva et al. (2017)	Norwegian commercial pilots - 12,552 pilot-years (2006 - 2010)	Medical reasons for grounding of 85 CAT pilots Rate: 6.8/1,000 pilot-years	Neurology Cardiovascular Psychiatric ENT Musculoskeletal	26% 18% 15% 15% 12%

Reference	Cohort/Data (study period)	Report based on:	Diagnostic category- frequency	
Jordaan (2017)	Loss of licence insurance of 65,000 professional pilots (Jan 2015-June 2016)	Medical reasons for claims concerning loss of licence	Musculoskeletal Cardiovascular Neurological Psychiatric Endocrine/Metabolic Neoplasms/cancer Digestive System	19% 18% 11% 10% 7% 7% 6%
Miura et al. (2002)	All Japanese pilots aged 60-63 with commercial licence (1991-2000)	Follow up of medical findings of 159 pilots who had additional tests at age 60	Cardiovascular Retired by the age ≤ 63 (unknown reasons)	4.4% 28%
Qiang et al. (2003)	3306 Male US Commuter and Taxi Pilots with Class 1 certificate (1987-1997)	Longitudinal study of mortality data	Death by Cancer Death by A/C crash Death by Cardiovascular Pilots 50-54 years had a 85% higher mortality risk than pilots of 45-49 years	34% 26% 18%
Zeeb et al. (2003)	6061 CAT pilots of 2 German airlines (followed 1960-1997)	Retrospective cohort study of cardiovascular mortality in pilots compared to general population	All Cardiovascular Death AMI <55 yrs AMI ≥55 yrs All other IHD	SMR 0.5 SMR 0.3 SMR 0.5 SMR 0.7
Kagami et al. (2009)	11,817 Japanese CAT pilots (2006)	Review of medical reasons of grounding of 767 pilots and detailed cardiovascular risk factor screening for pilots aged 60-64 yrs	Most frequent reasons for grounding tended to increase with age (non-significant) and were in decreasing order: 1. ophthalmological 2. malignancy 3. cardiovascular (no exact percentages provided in article)	
Linnersjö et al. (2011)	1478 active and retired Swedish CAT pilots (1961–1999 for mortality and 1987-1999 for AMI Incidence)	Follow up study of cardiovascular mortality and AMI incidence in pilots compared to general population.	All Cardiovascular death 40-49 yrs 50-59 yrs 60-69 yrs 70-79 yrs ≥80 yrs AMI Incidence 40-49 yrs 50-59 yrs 60-69 yrs 70-79 yrs ≥80 yrs	SMR 0.47 SMR 0.26 SMR 0.48 SMR 0.44 SMR 0.45 SMR 1.40 SIR 0.34 SIR 0.16 SIR 0.20 SIR 0.32 SIR 0.46 SIR 0.69

Reference	Cohort/Data (study period)	Report based on:	Diagnostic category- frequency
Sykes et al. (2012)	Survey of 595 CAT pilots New Zealand. (2009-2010)	Questionnaire on lifetime history of medical conditions for Study of pilot's health compared to health of general population	Pilots had lower rates of asthma, ischemic heart disease, depression, type 2 diabetes, anxiety, stroke, bowel disorders, prostate disease, and migraines, but a higher prevalence of kidney disease (3.3% vs 0.6%) and melanoma skin cancer (1.9% vs 0.04%) than the general population.

CAT=Commercial Air Transport; A/C=aircraft; SMR=Standardized Mortality Ratio; SIR=Standardized Incidence Ratio AMI=Acute Myocardial Infarction; IHD=Ischemic Heart Disease; CVD=Cerebrovascular disease.

In 2016, ICAO sent a survey to its Member States requesting information on medical causes of medium and long-term loss of licence (grounding six months to two years and two years or more) of professional pilots, general aviation pilots and air traffic controllers (Jordaan, 2017). Calculating the mean of the percentages of medium term and the long-term loss of licence, it was found that cardiovascular causes accounted for 23.5% of the cases, mental health for 22.5%, and neurology for 11.5%. The studies that assessed cardiovascular mortality and morbidity in CAT pilots (Zeeb et al., 2003; Linnersjö et al., 2011) provide convincing evidence that cardiovascular mortality and morbidity start increasing after the age of 50.

From the studies described above, it can be concluded that there is a high level of evidence that the most prevalent causes for long term unfit assessments are cardiovascular, neurological, psychological/psychiatric conditions (including problematic use of substances), and musculoskeletal conditions. Whilst musculoskeletal conditions are common causes of long term unfitness, they are not considered as a major cause of sudden incapacitation.

2.2.5 Outcome: age in relation to aeromedical disqualification rate

Årva and Wagstaff (2004) studied reasons for medical disqualification among the Norwegian commercial pilot population during a 20-year period (48,229 pilot-years). 275 Pilots were permanently grounded, which gave a 20-year mean disqualification rate of 5.7 per 1,000 pilot-years. It is remarkable that the disqualification rate (all diagnoses) in the age group ≥60 year is 5.74 which is nearly the same as the mean rate for the whole pilot population. Table 2.6 shows the cardiovascular, neurological, and psychiatric disqualification rates by age. It can be seen that the cardiovascular disqualification rate of those aged ≥60 is lower than the rates of the 40-49 and the 50-59 cohorts. It should, however, be considered that the ≥60 group includes only 6.5% of the total cohort while the other cohorts were much larger (15.1% in the 20-29 age group, 32.6% in the 30-39 age group, 25% in the 40-49 age group, 20.8% in the 50-59 age group). Neurological disqualification rates increased with age and were highest in the 50-59 age group (there were no cases in the ≥60 group).

Table 2.6 Age groups and cardiovascular, neurological, and psychiatric disqualification rates per 1,000 pilot-years (Årva & Wagstaff, 2004)

Age Group	Cardiovascular (35% of 275 cases)	Neurological (15% of 275 cases)	Psychiatric (13% of 275 cases)
20-29	0.3	0.4	0
30-39	0.7	0.5	0.6
40-49	3.0	0.9	1.6
50-59	4.0	2.0	0.8
≥60	2.5	0	0
Mean	**2.0**	**0.85**	**0.75**

Evans and Radcliffe (2012) analysed data of 16,145 UK/JAR professional pilot Class 1 license holders in 2004. A total number of 720 unfit notifications were analysed. Of the 720 pilot episodes of temporary unfitness, 670 were male and 50 female (658 ATPL, 56 CPL, 6 BCPL). The proportion of UK commercial pilots who were assessed as temporarily unfit was 4.3%. The unfitness rate demonstrated an increase starting in the 35-39 age group with a plateau until 49 years of age. Thereafter, there is a further increase to the highest values in the 50-54 age group with a marked drop after age 59 and further decrease in the 60-64 and 65-69 groups. The drop in the ≥60 years groups can be explained by the very low number of active pilots in these groups. This study nevertheless demonstrated an increased risk of unfitness with increasing age. A similar pattern was found in the age distribution of CAT pilot incapacitations (see Table 2.3).

Kagami et al. (2009) reviewed medical examination data of 11,817 CAT pilots in 2006. A total of 767 (7%) pilots were disqualified, and the rate of denials peaked between the ages of 50 and 59. The authors also reviewed all aeromedical and survey data of all Japanese CAT pilots over 60 years of age. Of the 326 respondents aged ≥60, 43% took voluntary retirement before reaching the Japanese age limit of 65 years. The average retirement age was 62.9 ± 1.3 year and 15% stated that they retired due to health reasons, with cardiac arrhythmia being the most common reason. The second most common reason reported was fatigue. Main reasons for grounding of the ≥60 cohort were - in decreasing order of frequency - visual problems, malignancy, coronary heart disease, cardiac arrhythmia, and cardiovascular disease. Since 1991 the Japanese Ministry of Transport allows medically certified airline pilots aged 60 to 63 to work on non-scheduled flights. By the end of 2000 Miura et al. (2002) analysed the medical follow-up data of 159 airline transport pilots who had undergone their first additional aeromedical examination at age 60. Thirteen pilots retired before reaching the age of 63 for unknown reasons. Five pilots were disqualified due to cardiovascular problems. Pilots aged 60-63 were not involved in any of the 27 air transport accidents reported in the past ten years.

From the studies above, it can be concluded that the most frequently reported disqualifying medical conditions associated with a potential incapacitation risk are age-related, and that the disqualification risk increases with increasing age. The assessment of the risk for pilots older than 60 years is hindered by the small numbers of active commercial pilots in most of the studies.

2.2.6 Conclusion of the literature analysis on incapacitation and medical fitness

In-flight incapacitation as a consequence of medical problems is a rare event occurring up to 0.45 times per 10^6 flight hours or 0.25% per annum. Most, but not all, authors found that the rate of incapacitations increases with increasing age. The level of evidence for the increase of incapacitations with age is considered to be moderate. Fifty to seventy percent of the medical incapacitations cannot be prevented by setting an age limitation because incapacitations caused by problems such as acute gastroenteritis, laser strikes, headache, and ear/sinus conditions are not age-related.

However, in the context of the question whether the regulatory age limitations can safely be extended beyond the age of 60, it is important to consider the medical conditions that bear an increased incapacitation risk and of which this risk increases with increasing age. The most frequently reported age-dependent medical conditions that led, or may lead, to total incapacitation are caused by cardiovascular, neurological, or psychiatric conditions and include sudden death, coronary artery disease, cardiac arrhythmias, pulmonary embolism, stroke (cerebral ischemic infarction, cerebrovascular accident, cerebral haemorrhage), syncope, late-onset seizure(s), and acute psychosis. Although not frequently reported, an acute renal stone event can be totally incapacitating, and therefore nephrolithiasis is added as a possible age-dependent cause of total in-flight incapacitation.

3 Analysis of Collected Data of Incapacitation of EU CAT Pilots

3.1 Commercial air transport

Data of accidents and incidents involving flight crew incapacitation in commercial air transport were obtained via EASA from ECCAIRS (European Co-ordination Centre for Accident and Incident Reporting Systems). The time period was 1970 through 2017. The following query was applied for a first selection of data:

{Narrative text {in any Narrative} [Word] like (ci) ‘incapacitation’
OR
Headline {Occurrence} contains ‘incapacitation’
OR
Narrative text {in any Narrative} [Word] like (ci) ‘consciousness’
OR
Narrative text {in any Narrative} [Word] like (ci) ‘sick’
OR
Expl factor subject {in any Explanatory factor} [Level 3] equal to Liveware (human) - Human physiology - Illness/Incapacitation
OR
Event type {in any Events} equal to Consequential Events - Damage and Injury Events - Medical and Injury - Medical/Incapacitation - Flight Crew
OR
Expl factor subject {in any Explanatory Factor} has at least one of Liveware (human) - Human physiology - Illness/Incapacitation - Mortality, Liveware (human) - Human physiology - Illness/incapacitation - Illness - Illness-food poisoning, [...]}

The initial data sample contained 501 occurrences. All occurrences from the sample were individually analysed to determine whether flight crew incapacitation was involved. Several duplications were identified and removed. For several occurrences, additional information was obtained from websites of accident investigation boards, most noticeably BEA (Bureau d'Enquêtes et d'Analyses pour la sécurité de l'aviation civile) and BFU (Bundesstelle für Flugunfalluntersuchung (BFU). Occurrences of incapacitation due to hypoxia, air quality, physical injury, barotrauma and exposure to a laser were removed from the sample. The sample also contained 29 occurrences without a narrative. For these 29 events, it could not be verified whether these were genuine occurrences of flight crew incapacitation and were therefore removed from the data sample. The resulting sample contained 257 occurrences of medical flight crew incapacitation events. Table 3.1 presents the distribution of events across type of incapacitation.

Table 3.1 Incapacitation occurrences by type. Commercial air transport

Type of incapacitation	Number of occurrences
Gastro-intestinal	35
Myocardial	27
Syncope	5
Cerebrovascular	4
Cancer	2
Diabetes	2
Epileptic	1
Psychiatric	1
Other illness	16
Unknown	164

The data sample contained information on the age of the incapacitated flight crew member for 63 of the 257 occurrences. It is remarkable that in the ECCAIRS database the cause of the medical incapacitation is unknown in 164 of the 257 occurrences. Figure 3.1 presents the cumulative frequency of the age of the pilots involved in the incapacitation events, for both the full sample of all types of incapacitation where the age of the crew member was reported (63 cases) and myocardial events where age of the crew member was reported (13 cases).

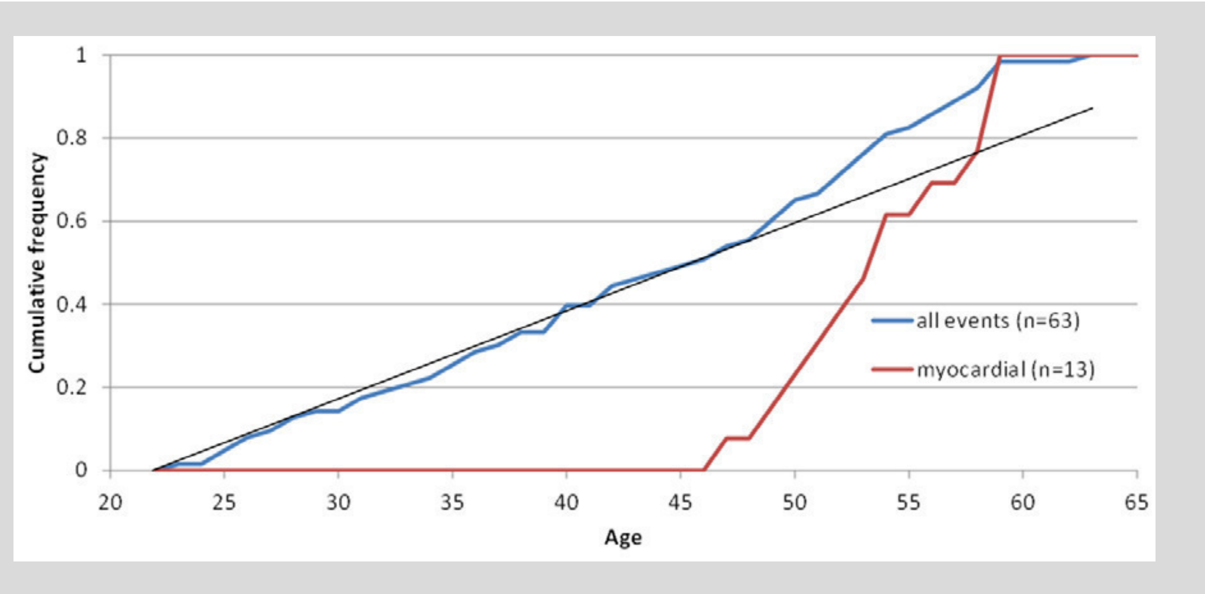


Figure 3.1 Age of pilots involved in in-flight incapacitation events. Commercial air transport, 1970-2017

For the total sample of incapacitation events the results show two 'regions' with an almost constant incapacitation probability. The first region ranges from age 20 to 45, the second region with a slightly increased incapacitation probability is from age 45 to 60. When the incapacitations due to myocardial events are separated out, it is noticeable that incapacitation due to myocardial events only occurs from the age of 45 onwards. However, this observation is based on a small sample of 13 events and therefore the statistical uncertainty is high. It should be noted that of the 27 occurrences, 16 (59%) involved incapacitation due to a myocardial event (see Table 3.1) resulting in death of the flight crew member. The fatality ratio of myocardial events is much higher than that of the other incapacitation events, where only 1 out of 230 (0.4%) resulted in a fatality.

3.2 General aviation

For commercial air transport, the pilot's age is in most states restricted by regulation to 65 years. Existing data on in-flight incapacitation for commercial air transport is therefore not necessarily suitable to estimate incapacitation likelihood for persons older than 65. On the contrary, for general aviation there are in most cases no strict pilot age limits. General aviation in-flight statistics could therefore be informative. Figure 3.2 presents the cumulative frequency of the age of the pilots involved in general aviation in-flight incapacitation events. This figure is based on US data only. Data were obtained from the NTSB aviation database (https://www.ntsb.gov/_layouts/ntsb.aviation/index.aspx) with the search engine directed to aircraft category 'airplane' and word string 'incapacitation'. From 2010 to 2017 there were 90 events that were individually analysed to determine whether flight crew medical incapacitation was involved. False positives were removed. The final sample consisted of 43 occurrences, involving 43 pilots.

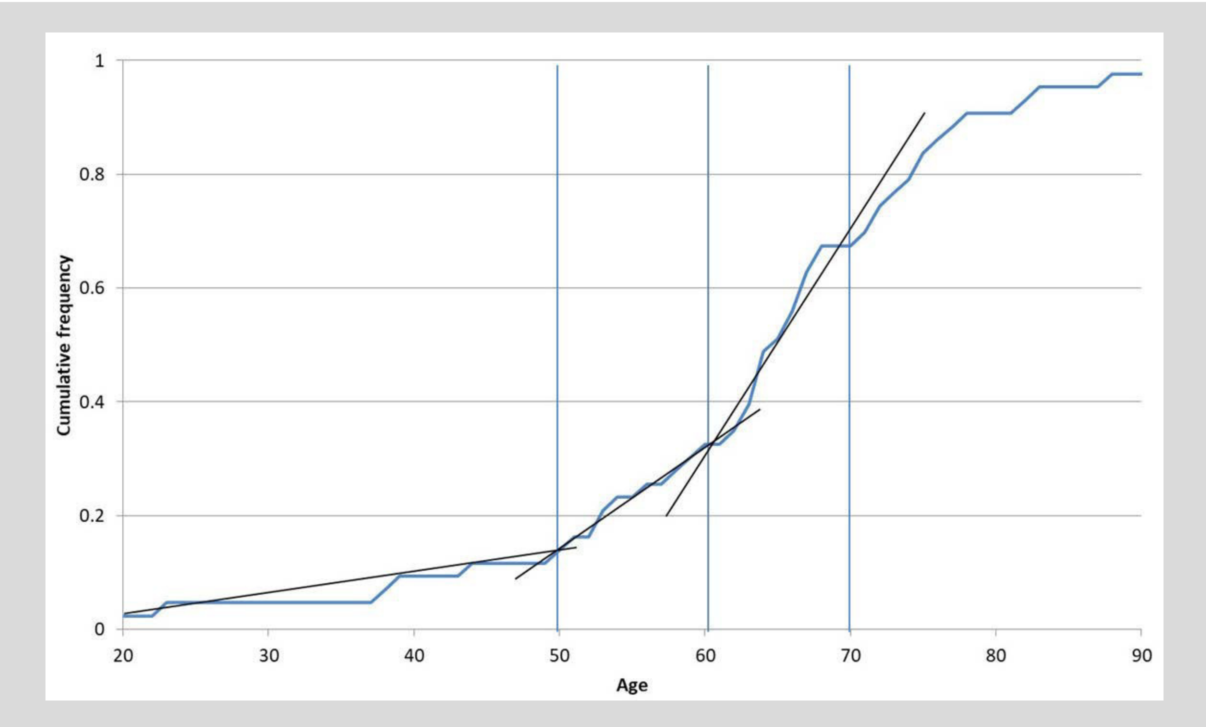


Figure 3.2 Age of pilots (n=43) involved in in-flight incapacitation events. US-FAA general aviation, 2010-2017

In Figure 3.2 three age classes can be distinguished that appear to have different incapacitation probabilities. The first group, with the lowest probability, is the 20-50 age group. From 50 to 60 the incapacitation probability is notably higher, and from age 60 onward the incapacitation probability is further increased. The curvature back to horizontal that can be observed in the figure for ages above 75 is probably an effect of exposure, there are simply not many pilots older than 75 and consequentially there are less incapacitation events. It must be noted that the medical requirements for general aviation pilots are less strict than those for commercial pilots. Of the 43 pilots included in the sample, only 9 (21%) held an FAA Class I or Class II medical certificate.
In contrast to the sample of commercial air transport pilot incapacitation events, the sample of general aviation pilot incapacitation events predominantly consist of myocardial events (Table 3.2) . This is most likely a result of the fact that myocardial events often lead to full incapacitation and therefore, in the case of single pilot operations, are catastrophic and as a result will be investigated by the NTSB. Additionally, myocardial disorders can in many cases be discovered post mortem. Gastro-intestinal disorders on the

other hand, may lead to discomfort but are rarely catastrophic and are therefore not investigated by the NTSB, while even in the case of a fatal outcome it is unlikely to be discovered (Booze, 1987). The fatality rate in this sample is high, 39 of the 43 accidents (91%) were fatal.

Table 3.2 Incapacitation occurrences by type. FAA General aviation 2010-2017

Type of incapacitation	Number of occurrences
Myocardial	29
Cerebrovascular	1
Cancer	1
Epileptic	1
Psychiatric	1
Other illness	2
Unknown	8

The analysis of ECCAIRS and NTSB databases provides evidence for a likely increase of in-flight incapacitation risk with increasing age. Moreover, the analyses show that myocardial events were the most frequent causes of in-flight incapacitations with a high fatality risk.

4 Analysis of Collected Data of Aeromedical Fitness of EU CAT Pilots in Relation to Age

4.1 Method

After consultation with EASA, obtaining the available medical evaluations data concerning CAT Pilots from European National Aviation Authorities (NAAs) began with an email by EASA to 18 preselected countries. Reminders were sent by EASA and TNO. Six countries supplied eligible data of good quality. The data represented the total number of pilots screened, their age, CAT category, and the number of pilots per subgroup that was declared unfit. In addition, the medical diagnoses for the individual cases that were declared (temporary) unfit were supplied as well.
The data of the six countries were pooled after which the Class 1 and Class 2 medical examinations were analysed. First, the association between age group, CAT class and unfitness was determined. Next, this was done for six types of medical indications we consider to bear the highest risk on incapacitation. Significant differences between age groups were determined using Chi^2 statistics.
Data concerning LAPL examinations were not included because

a. The cohort of pilots applying for a LAPL was considered to be insufficiently representative of commercial Class 1 pilots;
b. The requirements (and methodology of screening) for a LAPL are different compared to Class 1 and 2 requirements; and
c. Only a few responding NAAs provided detailed data concerning LAPL examinations.

It is acknowledged that Class 2 requirements for private pilots also differ from the Class 1 requirements for commercial pilots and that this cohort might not be completely comparable to commercial pilots. It was however decided to analyse the data concerning Class 2 examinations parallel to the Class 1 examinations because it was expected that this would enable an analysis of the age groups beyond 60 years. As is known, the number of pilots older than 60 years is low in the Class 1 cohort due to the existing age limit of 60 for single flying commercial pilots and the small number of airline pilots that are active in multi-pilot operations up to the age of 65.

4.2 Results

Table 4.1 represents the total number of pilots that were screened and the fraction of the pilots that were declared (temporary) unfit per age category and CAT class. A total of 50,101 Class 1 examinations and 32,334 Class 2 examinations were eligible to be included in the analysis. In Figure 4.1 the differences per age group and CAT class are depicted visually as well. It shows that among the 1,074 unfitness cases of Class 1 pilots the highest rate was found in 51-60 age category (4.4%; 370 cases) followed by the 61-65 and >65 age categories with both 3.0% (55 and 23 cases respectively). Among the 652 cases unfitness cases of Class 2 pilots the highest rates were found in the 61-65 category (2.9%; 96 cases) and >65 category (3.1%; 172 cases).
Figure 4.2 shows the absolute and relative contribution of six types of medical indications to the total number of (temporary) unfit declared pilots. Of the grand total of 82,435 examinations, 1,724 cases (2.1%) were found unfit. Cardiovascular conditions were the most frequent cause (19%), followed by psychiatric (11%), neurologic (10%), and psychological conditions (9%).
Figure 4.3 shows the differences in medical indications causing (temporary) unfitness between the different age groups. It can be seen that cardiovascular conditions are the most frequent reason for unfit-

ness in the older age groups with 21% (of 517 unfitness cases) in the 51-60 group, 28% (of 151 unfitness cases) in the 61-65 group, and 48% (of 195 unfitness cases) in those beyond 65 years of age. It is noteworthy that psychiatric and psychological reasons for disqualification were most frequent in the 20-40 age group.
Neurological reasons for unfitness were quite evenly distributed between all age groups. For all the other analysed medical conditions, the number of observed unfit cases per age group was significantly different (Chi² $p<0.05$) than was expected.

Table 4.1 Number of screened pilots per age category and class (pooled data)

AGE CAT	CLASS1	UNFIT (%)	CLASS2	UNFIT (%)	TOTAL	UNFIT (%)
20-40	24,149	358 (1.5%)	6.987	125 (1.8%)	31.136	483 (1.6%)
41-50	14,950	266 (1.8%)	7.569	112 (1.5%)	22.519	378 (1.7%)
51-60	8,396	370 (4.4%)	8.893	147 (1.7%)	17.289	517 (3.0%)
61-65	1,843	55 (3.0%)	3.347	96 (2.9%)	5.190	151 (2.9%)
> 65	763	23 (3.0%)	5.538	172 (3.1%)	6.301	195 (3.1%)
TOTAL	**50,101**	**1,072 (2.1%)**	**32,334**	**652 (2.0%)**	**82,435**	**1,724 (2.1%)**

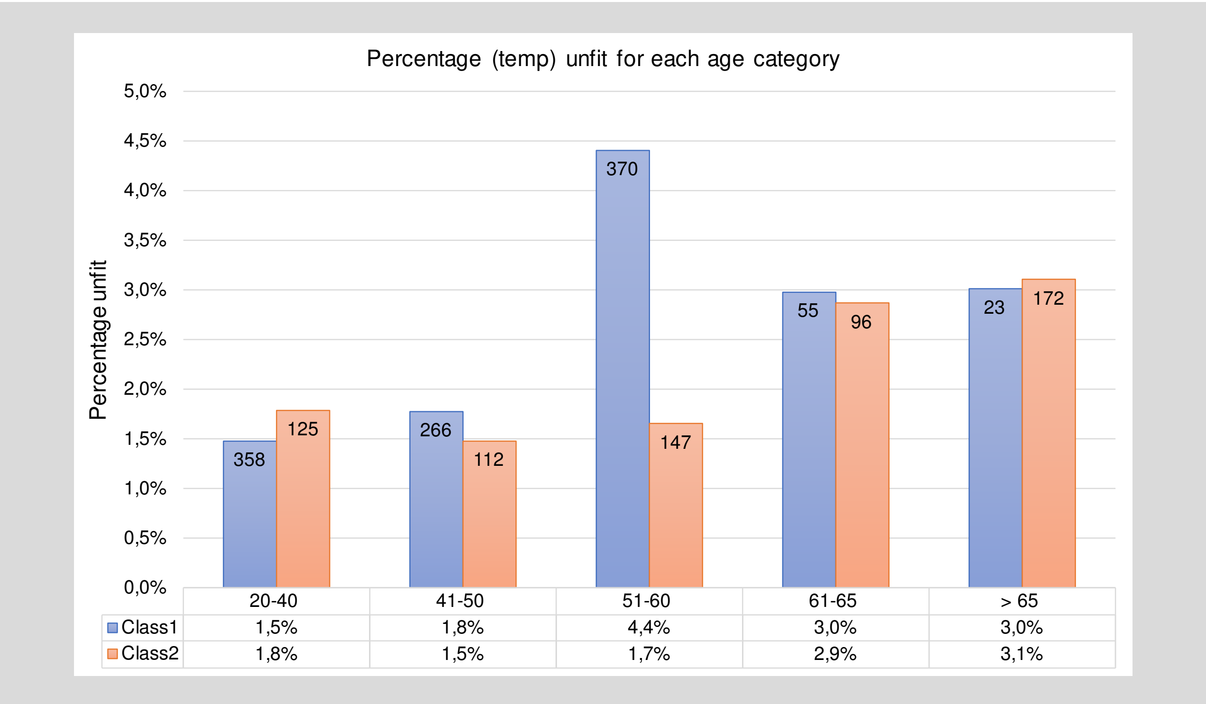
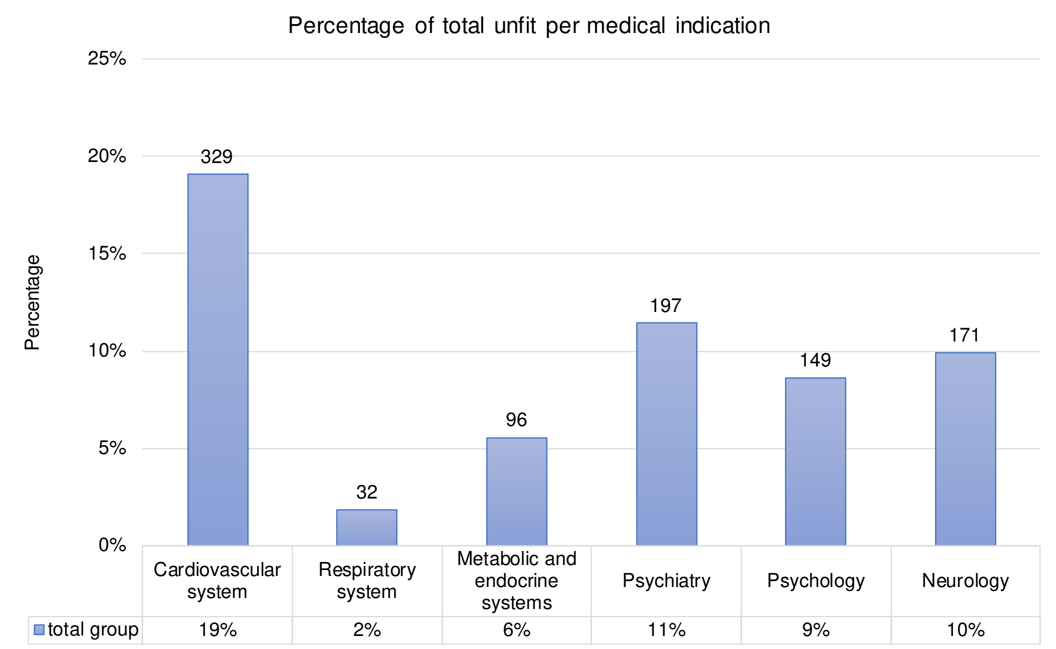
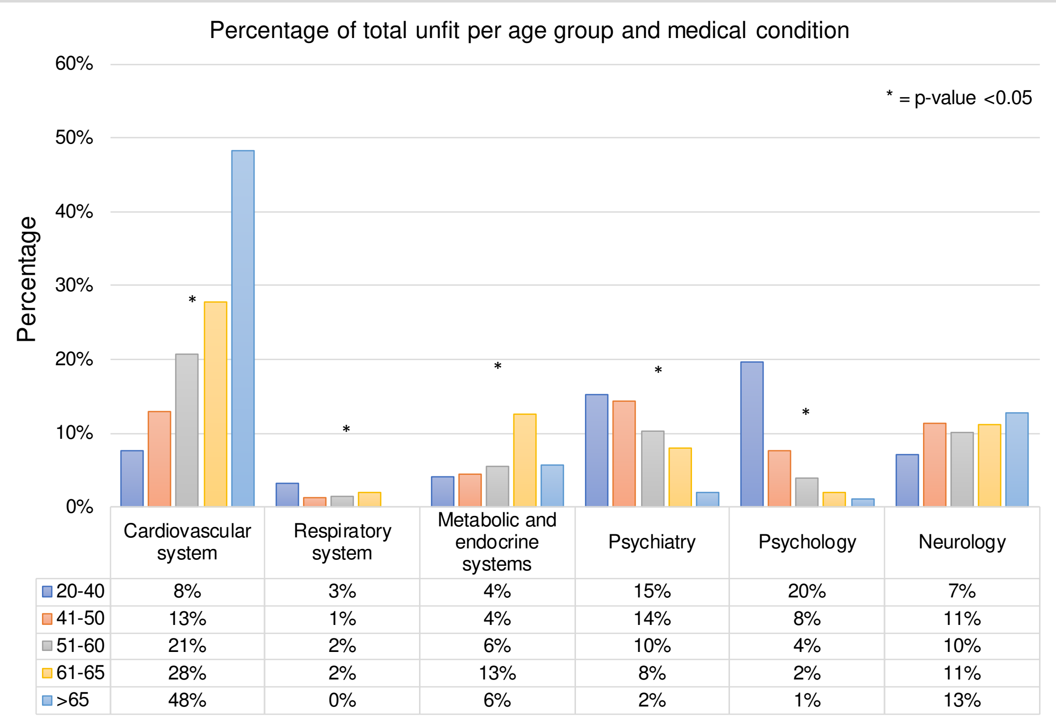


Figure 4.1 Visual representation of the pooled data of the examinations of Class 1 and Class 2 pilots



	Cardiovascular system	Respiratory system	Metabolic and endocrine systems	Psychiatry	Psychology	Neurology
total group	19%	2%	6%	11%	9%	10%

Figure 4.2 Absolute and relative contribution of six types of medical indications to the total number of unfitness cases



	Cardiovascular system	Respiratory system	Metabolic and endocrine systems	Psychiatry	Psychology	Neurology
20-40	8%	3%	4%	15%	20%	7%
41-50	13%	1%	4%	14%	8%	11%
51-60	21%	2%	6%	10%	4%	10%
61-65	28%	2%	13%	8%	2%	11%
>65	48%	0%	6%	2%	1%	13%

Figure 4.3 The relative contribution of six types medical indications to the total number of unfitness cases per age group

4.3 Discussion and interpretation

The geographical distribution of responding NAAs showed a balance Eastern, Western, Northern, and Southern European Member States. Therefore, we consider that the data analysed provides a fair representation of the European pilot population, thus minimizing known geo-epidemiological effects on certain diseases such as, for instance, ischemic heart disease and stroke. However, the analysis of the NAA data has some inevitable limitations as well. First, only six out of 18 NAAs were able and/or willing to provide us with qualitative data of pilot examinations. A larger response would have led to a more robust dataset and results that were better generalizable. In addition, when interpreting the differences between ≥60 pilot cohorts and younger pilot cohorts one should take into account that there may be a selection bias due to a possible healthy worker effect occurring in the ≥60 cohort. Next, although NAAs assignment of a medical category to the unfitness declaration will have been done by following the EASA rules laid down in Part Med, some medical conditions could have been assigned differently according to interpretation (e.g. syncope may be cardiovascular or neurological; moderately severe psychiatric conditions may be interpreted as psychiatric or psychological and vice versa). An asset of the present analysis is that the collected NAA data included considerably more cases of Class 1 pilots aged 61-65 (n=1,843) and >65 years (n=763) than comparable studies (Høva et al., 2017; Evans & Radcliffe, 2012; Kagami et al., 2009; Årva & Wagstaff, 2004; Miura et al., 2002). In these studies the low number of commercial pilots over 60 years of age was mentioned as a limitation of the study.
The results of the analyses coincide with the outcomes of the literature study on the most frequent reasons for (temporary) grounding of pilots (see Table 2.5 in Section 2.2.4 for the literature data), being cardiovascular, neurological, and psychological/psychiatric conditions. Among Class 1 pilots, the data of the current study showed, that there is a clear effect of increasing age on the medical disqualification rate with a more than doubling in the 51-60 age group compared to the 41-50 age group, followed by a slight decrease of the disqualification rate in >60 age groups. This slight decrease might be due to a healthy worker effect caused by self-selection and medical screening leaving the more physically and mentally fit older pilots in the workforce.
The results of the analyses also show that the most frequent reason for the grounding of pilots is a cardiovascular condition (19% of all reasons for grounding). This finding is in agreement with Årva and Wagstaff (2004) and Evans et al. (2001), who also found this as the leading medical condition, while Evans and Radcliffe (2012), Høva et al. (2017), and Jordaan (2017) found similar percentages for cardiovascular conditions (14%, 18%, and 18% respectively). The results of the present study show a significant increase of unfitness cases due to cardiovascular conditions with increasing age, which is in agreement with the age-dependent increase in cardiovascular mortality and morbidity of commercial pilots described in other studies (Zeeb et al., 2003; Linnersjö et al., 2011).

5 Risk Factors for Sudden Incapacitation and Their Relation to Age

To be able to interpret the results found in the previous sections, this section describes an analysis of the epidemiological literature on the effect of aging on medical conditions that have been found to bear a high risk to cause total in-flight incapacitation (sudden death, cardiovascular conditions, stroke, syncope, seizures, migraine, acute psychosis, and nephrolithiasis). This analysis is predominantly based on the general population and, if available, the pilot population is considered as well. In this context, it should be considered that active pilots are healthier and have a higher life expectancy than the general working population (Downey & Dark, 1992; Pizzi et al., 2008; Linnersjö et al., 2011). Moreover, the standardized risk of pilots to die from cardiovascular or cerebrovascular diseases - the main reasons for age-related sudden in-flight incapacitation - is significantly lower compared to the general population (Band et al., 1996; Blettner et al., 2003; Haldorsen et al., 2002; De Stavola et al., 2012; Qiang et al., 2003; Sykes et al., 2012; Hammer et al., 2014).

5.1 Sudden death

In the general population, the most common causes of sudden death are: fatal arrhythmias, acute myocardial infarction, intracranial haemorrhage/massive stroke, massive pulmonary embolism, and acute aortic rupture from aneurysm or dissection (AHA, 2018). Although causes of out of hospital sudden deaths cannot always be ascertained due to unreliability or absence of witnesses, there is convincing evidence that the great majority of sudden death cases are caused by cardiovascular reasons. The overall estimated incidence of sudden unexpected death may account for approximately 10% of all deaths classified as 'natural' (Lewis et al., 2016).

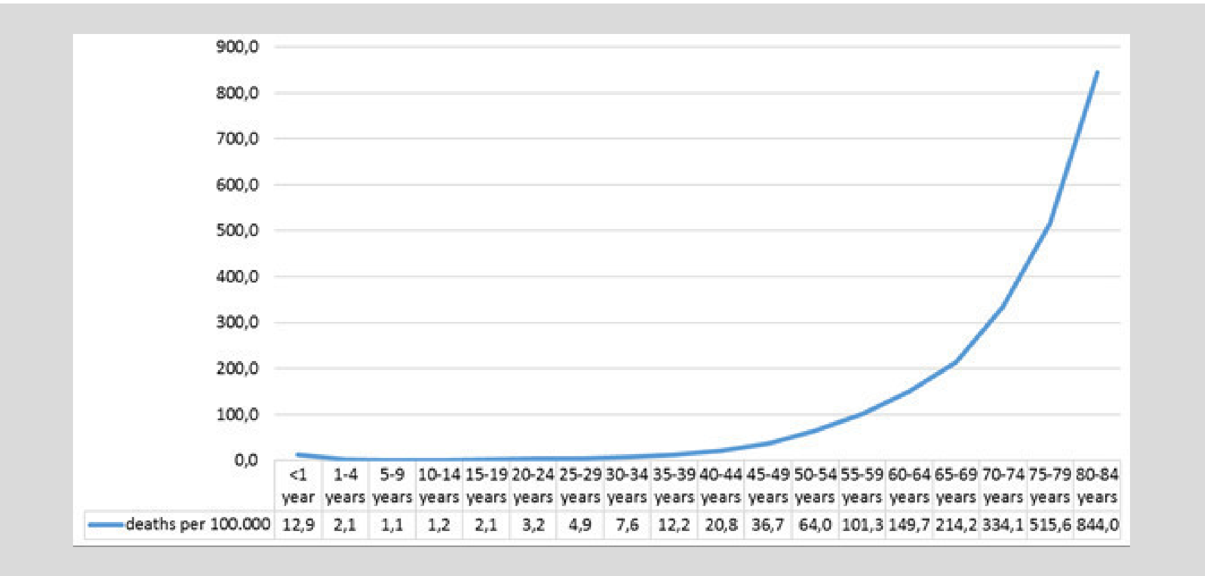


Figure 5.1 Death rates for any mention of sudden cardiac death by age in 2015 (number of deaths per 100,000 population). Data from Centers for Disease Control and Prevention WONDER (AHA, 2018)

Among adults, the risk of SCD increases exponentially with age (AHA, 2018; Figure 5.1) reaching 0.1-0.15% in the age group 55-64 and 0.2-0.3% in the ages 65-74. Sudden death will lead to a most unpredictable and complete incapacitation of a pilot. In case of single-pilot operation, there will be a complete loss of control of the aircraft.

5.2 Cardiovascular risk

Despite the much improved prevention and treatment options developed in the last decades, cardiovascular diseases remain a leading cause of morbidity and mortality in the general population (e.g., Baber et al., 2015). There is overwhelming evidence that cardiovascular risks increase with increasing age in the general population (e.g., AHA, 2018; Figure 5.2).

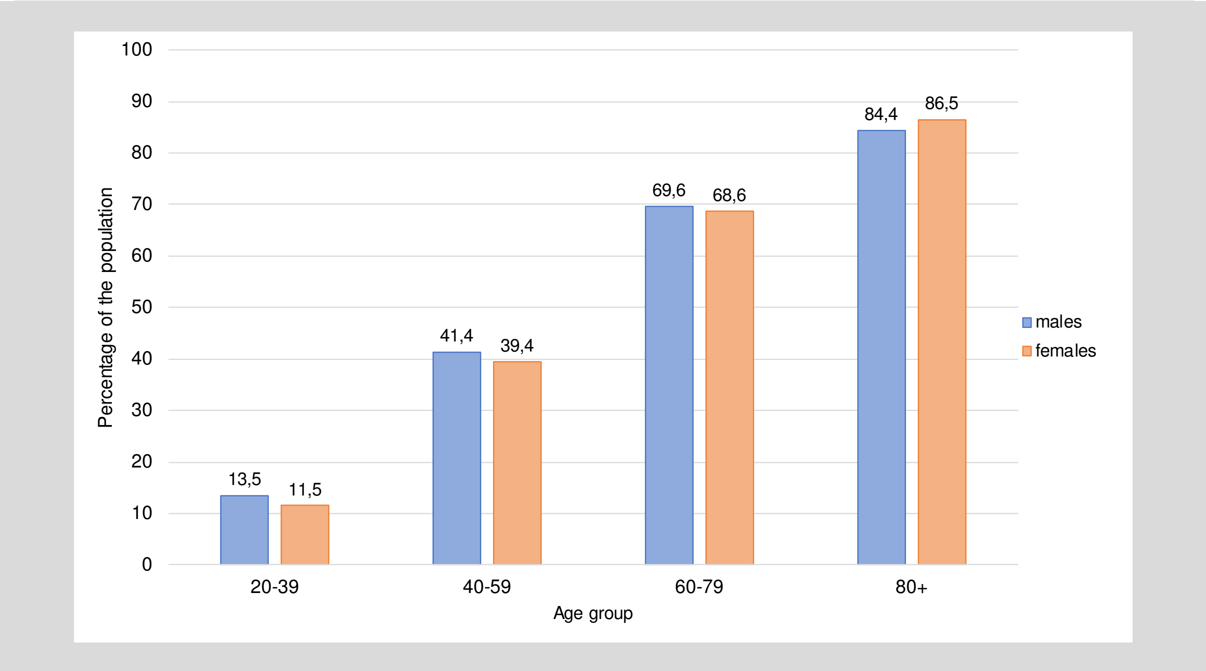


Figure 5.2 Prevalence of cardiovascular disease in adults by age and sex (National Health and Nutrition Examination Survey 2011-2014). Data include coronary heart disease, heart failure, stroke, and hypertension (AHA, 2018)

Death rates from ischemic heart disease (IHD) and stroke are generally higher in Central and Eastern Europe than in Northern, Southern and Western Europe, but cardiovascular mortality is currently decreasing in most European countries. Figure 5.3 shows the prevalence of cardiovascular diseases in different European countries.
Cohort studies from Canada, Great Britain, Italy, Norway, and Japan have demonstrated a lower cardiovascular mortality among professional pilots as compared to the general population. The Standardized Mortality Ratios (SMRs) ranged from 0.37 to 0.60 in these studies (Band, 1990; Band et al., 1996; Irvine & Davies,1999; Ballard et al., 2002; Haldorson et al., 2002; Kaji et al., 1993). Decreased cardiovascular mortality as compared to the general population is a common finding in occupational cohort studies and is a main indicator for the healthy worker effect (Zeeb et al., 2003; Qiang et al., 2003).

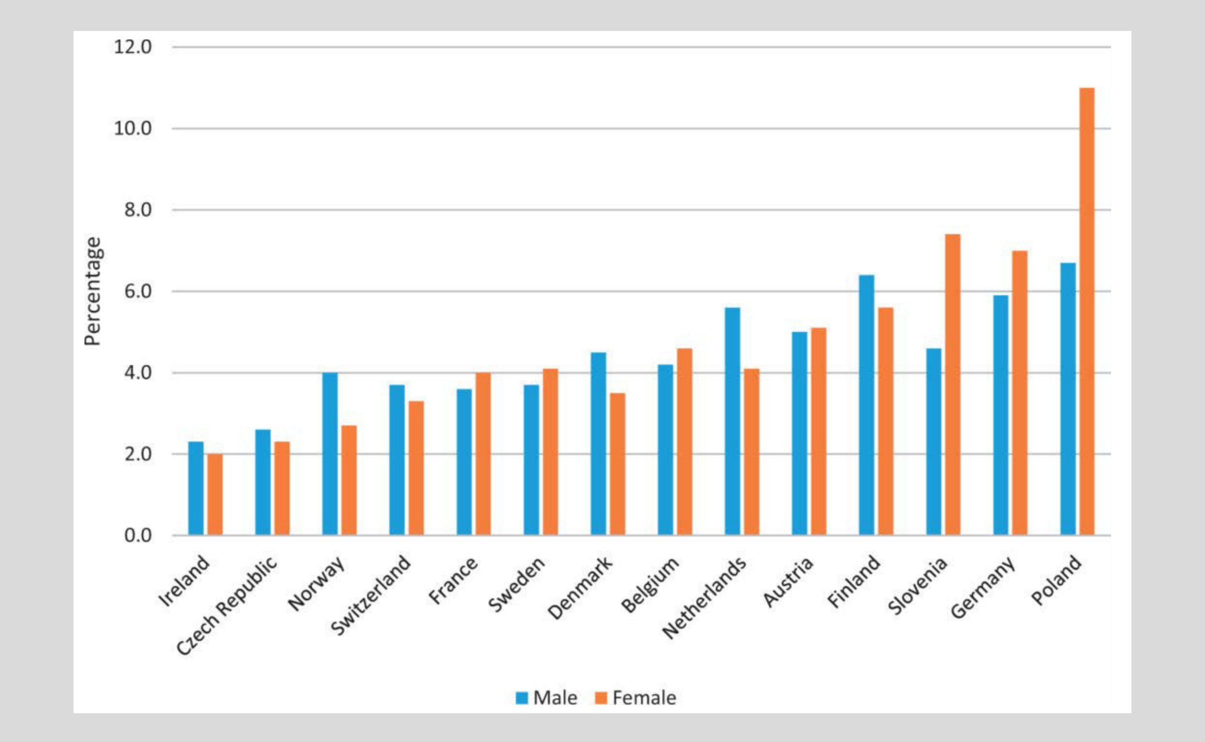


Figure 5.3 Percentage of European population reporting heart or circulation problems in the last 12 months, by country and sex in 2014. (Townsend et al., 2016)

Although the cardiovascular mortality rate in pilots is lower than in the general population, there is convincing evidence that the cardiovascular risk among pilots also increases with increasing age. This was, as mentioned in previous sections, shown by Zeeb et al. (2003) for 6,061 German CAT pilots, by Qiang et al. (2003) for a cohort of 3,263 FAA-certified commuter and air taxi pilots, and Linnersjö et al. (2011) for 1,478 Swedish CAT pilots (see Table 5.1), who also found an increase in the standard incidence ratio (SIR) of acute myocardial infarction (AMI) with increasing age. The SIR increased from 0.16 in 40-49 year old pilots to 0.20 in 50-59 year old, 0.32 in the 60-69 year old, and 0.46 in the 70-79 year old in the active and retired pilots.

Table 5.1 Estimated annual cardiovascular death risk UK commercial pilots (Mitchell & Evans, 2004)

Age group (yrs)	Risk (%)
20-24	0.004
25-29	0.006
30-34	0.012
35-39	0.030
40-44	0.063
45-49	0.129
50-54	0.255
55-59	0.470
60-64	0.824

Mitchell and Evans (2004) estimated the annual cardiovascular death risk of professional airline pilots by calculating the product of the number of licence holders flying public transport and the annual cardiovascular death risk of the general UK male population. The estimated annual cardiovascular death risk of UK professional pilots showed a clear increase of risk by age (Table 5.1). However, it should be considered that this annual cardiovascular death risk might be overestimated for pilots due to the fact that the authors used the cardiovascular risk data of the general male population for their estimation, while it is generally known that the cardiovascular death risk of professional pilots is considerably lower than that of the general population. Nevertheless, the increase of risk with advancing age holds. The cardiovascular death risk of professional pilots nearly doubles in every next higher age group, which mirrors the increase of cardiovascular mortality in the general population. The evidence for an age-dependent increase of cardiovascular risk among professional pilots is in agreement with the epidemiological data found in the current study, showing an age-dependent cardiovascular risk as is shown (e.g.) in Figure 5.1.

Pulmonary embolism (PE) is a relatively common acute cardiovascular disorder with high early mortality rates. Clinical data indicate that most cases of PE occur at 60 to 70 years of age, but autopsy data show the highest incidence among individuals 70 to 80 years of age (Bělohlávek et al., 2013). Patient risk factors include age, personal history of venous thromboembolism (VTE), active malignancy or other disabling conditions such as heart or respiratory failure, congenital or acquired coagulation disorders, hormone replacement therapy and oral contraception. Age is thought to be a risk factor due to an increase of incidence of other age-dependent risk factors for venous thromboembolism and PE (e.g., cardiovascular, immobility).

Considering above-mentioned cardiovascular conditions, it can be concluded that the cardiovascular disease risk

1. Is lower among active commercial pilots than among the general population, and
2. Increases with age with the largest increases from the age of 50 years onwards.

The fact that the annual cardiovascular death risk among active commercial pilots is lower compared to a general population of the same age can be explained by a strong healthy worker effect (diseased pilots will be disqualified, or may end their career), a good health status at the start of the career and early detection and intervention in case of abnormalities.

5.3 Stroke Risk (cerebral ischemic infarction, cerebrovascular accident, cerebral haemorrhage)

Globally, stroke is the second leading cause of (sudden) death after ischemic heart disease (Benjamin et al., 2018). Of all strokes, 87% are ischemic and 10% are intracerebral haemorrhage, whereas 3% are caused by subarachnoid haemorrhage (AHA, 2018). In the recent years there has been a remarkable decline in ischemic stroke (IS) mortality (Vaartjes et al., 2013), which is mainly due to timely treatment with tissue plasminogen activators (tPA) and endovascular procedures. However, the number of incidents of non-fatal IS events has remained stable (Vaartjes et al., 2013). In the context of sudden incapacitation, risk data of the incidence of IS are clearly more important than mortality data. Approximately 15% of all strokes are heralded by a Transient Ischemic Attack (TIA). The incidence of TIAs increases with age and TIAs confer a substantial short-term risk of stroke, hospitalization for CVD events, and death (AHA, 2018). Table 5.2 shows that the incidence of (first-ever) ischemic stroke (IS) in males starts to increase between 50 and 65 years of age and increases sharply in the age cohorts of 65-74 years and beyond.

Table 5.2 Incidence rates of Ischemic Stroke

Reference	Population	Metric	Age group	Rate
Vangen-Lønne (2015)	Norway 36,575 participants of the Tromsø Study. (2006-2010)	Incidence per 1,000 person-years (py)	30-49 50-64 65-74 75-84 >85	0.7/1,000 py 2.2 6.6 17.5 25.6
Rosengren et al. (2013)	391,081 stroke cases Swedish population from 18 - 84 years 1987-2010	Incidence first-ever stroke (percentage)	18-44 45-54 55-64 65-74 75-84	0.01% 0.06% 0.21% 0.61% 1.52%
Vaartjes et al. (2013)	Admitted IS patients in The Netherlands (1997-2007)	Incidence ischemic stroke (percentage)	35-64 65-74 75-84	0.08% 0.40% 0.94%
AHA (2018)	1.3 million, all incident strokes in Greater Cincinnati/Northern Kentucky Stroke Study (USA 1994-2010)	Incidence of first ischemic stroke in white males (percentage)	45-54 55-64 65-74 75-84 >85	0.11% 0.27% 0.76% 1.25% 3.21%

5.4 Syncope Risk/Loss of consciousness (LOC)

Syncope is the sudden loss of consciousness, associated with inability to maintain postural tone, with immediate and spontaneous recovery without requiring electrical or chemical cardioversion. Syncope is caused by insufficient cerebral perfusion and the resulting loss of consciousness has a short duration (average 12 seconds) (da Silva, 2014). Among the causes of syncope, the neurocardiogenic or vasovagal syncope is the most frequent. The other causes are of cardiac origin, orthostatic hypotension, carotid sinus hypersensitivity, neurological, endocrinological, and psychiatric disorders. The incidence of syncope is difficult to estimate because many cases might occur outside the hospital and are therefore not referred to medical care and/or registration by health authorities. In the general population, syncope has an estimated annual incidence rate of 6% (Moya et al., 2009) with similar incidence between genders, and with highest prevalence between 10 and 30 years of age (mainly as a result of vasovagal syncope). There is a significant increase in the incidence of syncope after 70 years of age, with 5.7 episodes/1,000 individuals per year between 60 and 69 years old and with 11.1 episodes/1,000 individuals per year between 70 and 79 years age. After 80 years, the annual incidence may reach 19.5 per 1,000 individuals (Moya et al., 2009).

5.5 Neurologic risk: late-onset seizure(s) risk (epilepsy, seizure)

Epileptic seizure is regarded as an important cause of total incapacitation. A seizure occurs suddenly and is usually accompanied by spasms, muscular cramp and loss of consciousness (grand mal). In a few cases, the seizure is confined to contractions of the muscles (petit mal) or simply to a twilight state of the active consciousness (absence). Clearly, all three forms of epileptic seizure cause incapacitation, and a case of grand mal in the cockpit will cause major problems.
Age affects the incidence rate of epilepsy, with the highest incidence in the very young and very old groups. The incidence rate in children younger than 1 year is 100-233 per 100,000. The rate decreases

in people aged 20-60 years to 30-40 cases per 100,000, and then increases to 100-170 cases per 100,000 in people older than 65 years (Hesdorffer et al., 2011). Age also plays a part in terms of the cause. At a younger age, the cause is usually ‘idiopathic’ or ‘spontaneous’ (unknown cause) or traumatic, but in older people epileptic seizures are often caused by vascular diseases or by tumours and metastatic growths in the brain (Sander et al., 1990). Other (preventable) causes of epileptic seizures may be lack of sleep and alcohol abuse (especially abstinence after excessive consumption) (Simons et al., 1996). The incidence of new seizures is approximately constant, at least up to 65 years of age. For a population of 10,000 pilots with an annual risk of 0.05%, and an average time in the air of 500h (1/20 of the year), 0.25 in-flight seizures might be expected per year (10,000 x 0.05% x 1/20) (Mitchell & Evans, 2004). Although Mitchell and Evans (2004) rightly considered that the occurrence of a first seizure cannot be accurately predicted in an individual, either by investigation or age-based risk estimation, the risk is considered to be increased when there is evidence for cerebrovascular diseases.

5.6 Neurologic risk: migraine

Migraine is a common disorder, affecting about 11% of adult populations in Western countries. The prevalence is significantly higher among women than among men. Prevalence is highest between the ages of 25 and 55 and peaks between 10 to 35 years of age (Stewart et al., 2008; Victor et al., 2010).

5.7 Psychiatric risk: acute psychosis; major depressive disorder

Most new cases of psychosis arise in men under 30 and women under 35, but a second peak occurs in people over 60 years (Brugha et al., 2005). The latter peak includes degenerative brain processes and non-affective psychosis. Van Os et al. (1995) examined the association between ageing and the incidence rate of late-onset (after age 59) non-organic, non-affective psychosis in two samples of patients aged 60 years or older who were first admitted to hospital in The Netherlands and Great Britain between 1976 and 1992 (total n = 9,787). A linear trend was found in the association between increasing age and first admission rates for non-organic, non-affective psychosis in the elderly, corresponding to an 11% increase in the incidence with each 5-year increase in age. These observations support a connection between degenerative brain processes and onset of non-affective psychosis in the elderly. The number of subjects displaying incident psychotic symptoms was similar across age groups.

Major Depressive Disorder can develop at any age, the median age at onset is 32.5 years old and the prevalence of adults with a major depressive episode is highest among individuals aged between 18 and 25. Rates of depression differ considerably between countries and women reported higher rates of depression in all countries. There is no significant evidence for increasing risk of depressive disorder with increasing age (WHO, 2017; ISD Scotland, 2012).
Suicide rates show no increase in the higher age groups, except in those aged over 85 years. In the UK, the age groups with the highest suicide rate per 100,000 are: 40-44 years for males and 50-54 years for females (Scowcroft, 2017).

5.8 Nephrolitiasis (renal stones)

Although not frequently reported, an acute renal stone event can be totally incapacitating. The prevalence of nephrolithiasis and the relation with age differs widely between different countries and continents (Sorokin et al., 2017). Most studies found a significantly lower prevalence in women than in men and an increase of kidney stones with increasing age. In the US population, Scales et al. (2012) found a prevalence for men of 3.1% in 20-29 year old adults, which increased to 6.9% (30-39 yrs), 9.8% (40-49 yrs), 13.1% (50-59 yrs), and peaked in 60-69 year old adults at 19.1% and remained fairly stable at 18.8% in men over 70 years of age.

6 Discussion and Conclusion: Synthesis Based on the Results of Sections Above

In-flight incapacitation as a consequence of medical problems is a rare event occurring up to 0.45 times per 10^6 flight hours or 0.25% per annum. The literature study in this project provided moderate evidence that the incapacitation rate increases with age. This concurs with the outcome of the analysis of data of the ECCAIRS system on incapacitation of EU CAT Pilots, as well as with the data of the NTSB database. It was also found that the more serious medical conditions that can cause sudden incapacitation occur in the older age groups. Fifty to seventy per cent of the medical incapacitations, however, cannot be prevented by setting a regulatory age limit because incapacitations caused by problems such as acute gastroenteritis, laser strikes, headache, and ear/sinus conditions are not age-related.
In the context of the question whether the regulatory age limitations for all CAT pilots can safely be extended, only the medical conditions that include an increased incapacitation risk with increasing age should be considered.

The literature review of the medical reasons for disqualification provided evidence that the most frequently reported age-dependent medical conditions that led to grounding of the pilot are cardiovascular, neurological, or psychiatric conditions. This is in agreement with the outcome of the analyses of the available medical evaluations data concerning CAT Pilots from European National Aviation Authorities (NAAs). These findings are further supported by the analysis of the medical reasons of sudden incapacitations in which the most frequent causes of sudden incapacitation include sudden death, coronary artery disease, cardiac arrhythmias, pulmonary embolism, stroke (cerebral ischemic infarction, cerebrovascular accident, and cerebral haemorrhage), syncope, late-onset seizure(s), and acute psychosis.
The emphasis placed on the prediction of sudden cardiac death, cardiovascular, and cerebrovascular events by aviation regulators by screening for underlying risk factors appears to be well founded. The increased risk of incapacitation from these disorders with age is clearly demonstrated, although Bauer et al. (2018) found no indication of a worsening cardiometabolic risk marker profile in HEMS pilots as they approached the age threshold for single-pilot commercial air transport operations of 60 years compared to younger pilots. A major and inevitable limitation of this study was, however, its small sample size and the associated large estimation uncertainty, especially regarding the critical group of pilots aged ≥60, which consisted of only 10 pilots.
Although not in the context of the current research task in which only total incapacitation was to be considered, it should be considered that inadequate pilot performance is a causal factor in 35-75% of accidents (e.g. Baker et al., 1993; Li et al., 2002). Interpersonal variance in cognitive and job performance usually increases with progressing age (Salthouse, 2004), but the likelihood of pilot-error incidents decreases with experience (Li et al., 2001; 2003; McFadden, 1997). A decision should therefore not solely be based on the medical fitness, but also on other aspects like individual cognitive and sensory performance in order to generate a more complete picture of the pilot's ability to fly safely.

Conclusion/Recommendation

The results of the present literature review, the analyses of the collected NAA data, and data of the ECCAIRS system in relation to age, indicate that it is appropriate to concentrate surveillance of pilots at greatest risk of cardiovascular and cerebrovascular medical events, especially those over the age of 50. The findings of the present task will be used in Task 2 and Task 3. In Task 2, the age-dependent estimated incapacitation risk rates, derived from literature, will be used for the assessment of incapacitation risk levels as a function of pilot age in comparison with risk acceptability thresholds. In Task 3, the screening procedures and underlying risk factors concerning sudden death, coronary artery disease, cardiac arrhythmias, pulmonary embolism, stroke, syncope, late-onset seizures, and psychosis will be discussed.

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Part 2 Risk Assessment Based on Operations Considerations (Deliverable No. 2)

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Content Part 2

1 Introduction

The first phase of this research study (Simons et al., 2018) concluded that in the context of the question whether the regulatory age limitations for all CAT pilots can safely be extended, the medical conditions that include an increased incapacitation risk with increased age should be considered. The study also concluded that the emphasis placed on the prediction of sudden cardiac death, cardiovascular and cerebrovascular events by aviation regulators by screening for underlying risk factors appears to be well founded. The increased risk of incapacitation from these disorders with age is clearly demonstrated.
In the second phase of the research study, described in this report, flight crew incapacitation probabilities are estimated as a function of flight crew age and are compared with established risk acceptability thresholds. The estimates of flight crew incapacitation probabilities are based on age-dependent estimated mortality risk rates and hospital admission rates described in literature.

2 Method

2.1 General description

The approach for determining risk levels and comparison with acceptability criteria is similar to the approach applied for aircraft system safety assessments as described in aircraft certification specifications (CS). For large aircraft, requirements for system safety assessments are described in CS 25.1309 and the accompanying acceptable means of compliance (AMC). This is essentially a risk based approach, providing requirements for a logical and acceptable inverse relationship between the probability and severity of a failure condition. Whereas the failure conditions in CS 25.1309 refer to system failures, we apply this approach to pilot incapacitation events.
Current aircraft system failure probability requirements are based on the principle of an inverse relation between the probability of a system failure and the consequence of the failure.
According to the requirements for large aircraft (CS 25.1309 or equivalent), catastrophic failure conditions must be extremely improbable. Catastrophic failure conditions are failure conditions which would result in multiple fatalities, usually with the loss of the aeroplane. Extremely improbable failure conditions are those having a probability lower than $1x10^{-9}$ per flight hour.
Hazardous failure conditions must be extremely remote. Hazardous failure conditions are failure conditions which would reduce the capability of the aeroplane or the ability of the crew to cope with adverse operating conditions to the extent that there would be:

1. A large reduction in safety margins or functional capabilities;
2. Physical distress or excessive workload such that the flight crew cannot be relied upon to perform their tasks accurately or completely; or
3. Serious or fatal injury to a relatively small number of the occupants other than the flight crew.

Extremely remote failure conditions are those having a probability between $1x10^{-7}$ and $1x10^{-9}$ per flight hour.
Major failure conditions must be remote. Major failure conditions are failure conditions which would reduce the capability of the aeroplane or the ability of the crew to cope with adverse operating conditions to the extent that there would be, for example, a significant reduction in safety margins or functional capabilities, a significant increase in crew workload or in conditions impairing crew efficiency, or discomfort to the flight crew, or physical distress to passengers or cabin crew, possibly including injuries. Remote failure conditions are those having a probability between $1x10^{-5}$ and $1x10^{-7}$ per flight hour.
Single pilot operations in commercial aircraft may only be carried out in small aircraft, i.e., aircraft that are certified under EASA CS 23 or equivalent. According to CS 23.2510, any catastrophic failure condition must be extremely improbable. Numerical values of the associated probability vary from $<1x10^{-9}$ to $<1x10^{-6}$, depending on the complexity of the aircraft (ASTM F3230).

2.2 Likelihood estimation

Results of Task 1 will be used to estimate the likelihood of sudden and complete pilot incapacitation as a function of pilot age. The likelihood is expressed as an average probability per flight hour.

2.3 Severity estimation

The severity of a sudden and complete incapacitation depends on the number of flight crew. A sudden and complete incapacitation of a pilot in a multi pilot operation can be considered a major failure condition. A sudden and complete incapacitation of a pilot in single pilot operations can be considered a catastrophic failure condition.

3 Estimating Flight Crew Incapacitation Rates from Reported In-flight Incapacitation Events

Ideally, flight crew incapacitation probabilities are estimated from data on in-flight incapacitation events. However, literature on in-flight incapacitation is scarce and suffers from lack of consistency concerning the definition of incapacitation.
DeJohn et al. (2004) defined in-flight medical incapacitation as a condition in which a flight crew member was unable to perform any flight duties and impairment as a condition in which a crew member could perform limited flight duties, even though performance may have been degraded. Based on data from a six-year period (with 39 incapacitations and 11 impairments aboard 47 aircraft), the average incapacitation rate, across all ages, was $4.5x10^{-7}$ per flight hour according to DeJohn et al. (2004). A limitation of this study is a lack of data for flight crew older than 59 years and a lack of information about the speed of onset of the incapacitation. It is based on data collected before 2005 and, therefore, the results might not completely reflect the current public health level.
Deliverable 1 of this study (Simons et al., 2018) presents the results of an analysis of worldwide data of accidents and incidents involving flight crew incapacitation in commercial air transport that were obtained via EASA from the European Central Repository for accident and incident reports in aviation. From 1990 to 2017, there were 200 reported pilot flight crew incapacitations worldwide. According to the NLR Air Safety Database, worldwide commercial air transport from 1990 to 2017 accumulated a total number of 1,397 million flight hours, resulting in an average incapacitation rate of $1.43x10^{-7}$ in-flight incapacitations per flight hour with no significant yearly trend apparent. The data sample from the European Central Repository for accident and incident reports in aviation only contained information of the age of the incapacitated pilot in 25% of the sample. The type of medical incapacitation is unspecified in 64% of the data sample. Information on the degree of incapacitation is completely absent. The limitations of the data on in-flight incapacitation events render them unsuitable for reliable estimation of in-flight incapacitation probabilities as a function of pilot age.

According to the International Air Transport Association (IATA), from Q1 2014 to Q4 2017, a total of 324 reports were found in IATA's Safety Trend Evaluation, Analysis and Data Exchange System (STEADES) database related to flight crew incapacitation (IATA 2018). The STEADES database is comprised of de-identified safety incident reports (Air Safety Reports ASR and Cabin Safety Reports CSR) from over 200 participating airlines throughout the world, with an annual reporting rate exceeding 200,000 reports per year. According to the NLR Air Safety Database, worldwide commercial air transport from 2014 to 2017 accumulated a total number of 339 million flight hours, resulting in an average incapacitation rate of $9.55x10^{-7}$ in-flight incapacitations per flight hour. A total of 26 reports stated that ATC was informed (PAN or Mayday) due to the severity of the flight crew incapacitation. This corresponds with a rate of $4.17x10^{-7}$ severe pilot incapacitations per flight. Note that this number corresponds well with the incapacitation rate presented by DeJohn et al. (2004).

Evans and Radcliffe (2012) estimated pilot incapacitation rates from a combination of unfit notifications, occurrences reports and notifications of sudden death of UK commercial pilots in 2004. According to these data, the incapacitation rate varies from $1.26x10^{-7}$ per flight hour for the 20-29 age group to $1.37x10^{-6}$ for the 60-69 age group, with an average incapacitation rate of $2.85x10^{-7}$ per hour. A limitation of this study is the small sample size (40 incapacitations) and that it is based on data collected before 2005 and, therefore, the results might not completely reflect the current public health level.

4 Flight Crew Incapacitation Rates from Population Mortality Rates and Hospital Admission Rates

4.1 Justification

Results from a literature review presented in Deliverable 1 of this study (Simons et al., 2018) showed that fifty to seventy percent of medical incapacitations are not age related. Examples of non-age related incapacitation events are acute gastroenteritis, laser strikes, headache and ear/sinus conditions. Age related incapacitation events are sudden cardiac death, cardiovascular and cerebrovascular events. In Deliverable 1 it is concluded that sudden and complete incapacitation is caused by cardiovascular or cerebrovascular events.
To estimate incapacitation rates as a function of pilot age, it is considered to use the general population mortality rate for all cardiovascular conditions as a lower estimate, and to use the general population hospital admission rate as an upper estimate. We then apply a reduction factor based on the literature data concerning the Standardized Mortality Ratio of commercial air transport pilots compared to the general population mortality. It is considered reasonable to use the cardiovascular epidemiological data of the Netherlands because the Dutch data represent an average of the European population reporting heart or circulation problems (Townsend et al., 2016). A comparison of Netherlands data on ischemic heart disease with mortality from ischemic heart disease for different regions (Finegold et al., 2012) confirms this assumption.
Male mortality and hospital admission statistics are used for the analysis. Although the pilot population includes both men and women, the majority of current commercial pilots are male. Because cardiovascular risk is lower in women under 65 year of age, using male cardiovascular risk will overestimate risk in the total population (Mitchell & Evans, 2004).

4.2 Lower estimate

According to Tunstall-Pedoe (1984), the cardiovascular mortality rate can be taken to approximate the cardiovascular incapacitation rate. Although the incapacitation rate is expected to be higher than the mortality rate since incapacitation cardiovascular symptoms do not necessarily result in death, this is balanced by the number of cardiovascular deaths which do not pose an in-flight incapacitation risk because the pilot has developed symptoms or a disease which results in grounding without causing an incapacity (Mitchell & Evans, 2004).

4.3 Upper estimate

When estimating risk of in-flight incapacitation, rates of hospital admission[1] may be more relevant than mortality rates; i.e. nowadays many myocardial infarctions are successfully treated by percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG). These patients do not die whereas the pre-hospital symptoms of their myocardial infarction or acute coronary syndrome may represent a high likelihood of acute incapacitation. This reasoning is supported by Jørstad et al. (2016). The percentage of hospital admissions due to myocardial infarction is considered to represent all cases of myocardial infarction (MI) and acute coronary syndrome (ACS), because in the Netherlands

[1] Hospital admission is defined as stay in the hospital; all outpatient diagnostics/treatments are excluded.

99% of the MI or ACS cases will be admitted to a hospital, due to the easy reachability and accessibility of the hospitals. A similar reasoning applies to stroke risk; the first-ever or new cases of stroke might not be fatal but can cause total incapacitation, while established or repeated stroke cases are likely to preclude commercial flying activities.
Therefore, Table 4.1 presents general Netherlands male population mortality rates and hospital admission rates for all cardiovascular conditions including ischemic heart disease, myocardial infarction and stroke mortality. Rates are expressed as percentage per year. Heart failure data are not included here because heart failure is not considered to be a risk factor for in-flight incapacitation as it is a chronic condition leading to incapacitation in the patient's daily life and precluding flight duties.

Table 4.1 General Netherlands population male mortality rates for all cardiovascular conditions excluding heart failure and hospital admission rates for myocardial infarction/acute coronary syndrome and new cases of stroke in 2016 (Buddeke et al., 2017)

Age category	Mortality rate cardiovascular conditions	Hospital admission rate myocardial infarction + first stroke
25-34	0.002	0.052
35-44	0.002	0.052
45-54	0.020	0.457
55-64	0.106	0.907
65-74	0.296	1.431
75-84	0.927	2.258

Standardized cardiovascular mortality ratios (SMRs) as well as the standard incidence ratios (SIRs) of acute myocardial infarction of commercial pilots presented in literature (Linnersjö et al., 2011; Zeeb et al., 2003; Irvine & Davies, 1999) are typically in the order of 0.5 compared to the SMRs and SIRs of the general population with a very slow decline of this reduction of SMRs with high age, indicating a slowly decreasing healthy worker effect. For the purpose of this study a value of 0.5 will be used as a reduction factor for the lower estimate of the incapacitation rate (based on cardiovascular mortality) while a factor of 1.0 will be used for the upper estimate of the incapacitation rate (based on the hospital admission rate).
The general population cardiovascular mortality rates and hospital admission rates with the reduction factor provides the lower and upper estimates of the probability per hour of sudden and complete pilot incapacitation as presented in Table 4.2 and Figure 4.1[2]. Under the assumption that a year contains 8,760 hours, these yearly percentages can be expressed as probability of occurrence per hour. In this calculation it assumed that pilot cardiovascular mortality rates and hospital admission rates are evenly distributed across the year, i.e., no seasonal effects.

Table 4.2 Estimated probability per hour of sudden and complete pilot incapacitation

Age category	Pilot incapacitation probability per hour - lower estimate -	Pilot incapacitation probability per hour -upper estimate -
25-34	$1.14x10^{-9}$	$5.94x10^{-8}$
35-44	$1.14x10^{-9}$	$5.94x10^{-8}$
45-54	$1.14x10^{-8}$	$5.22x10^{-7}$
55-64	$6.05x10^{-8}$	$1.04x10^{-6}$
65-74	$1.60x10^{-7}$	$1.63x10^{-6}$
75-84	$5.29x10^{-7}$	$2.58x10^{-6}$

2 Note that Figure 4.1 has a logarithmic vertical scale.

Figure 4.1 Estimated probability per hour of sudden and complete pilot incapacitation

5 Comparison of Flight Crew Incapacitation Probability with System Failure Probability Requirements

5.1 Multi pilot operation

Current aviation certification specifications for commercial air transport do not prescribe pilot incapacitation probability limits. A comparison with aircraft system safety requirements, as defined in CS 25.1309 is made to derive plausible limits for pilot incapacitation. In a 2-pilot crew, sudden and complete incapacitation of one pilot will result in a significant reduction in functional capabilities and a significant increase in crew workload. It is therefore a major failure condition and must be remote, i.e. the probability must be between $1x10^{-5}$ and $1x10^{-7}$.
Note that the “1% rule”, an annual medical incapacitation risk limit of 1% that has been applied over the last decades in Europe, corresponds to an incapacitation probability of $1.14x10^{-6}$ per flight hour.
Figure 5.1 presents the estimated pilot incapacitation probabilities as a function of age in relation to probability thresholds for system failures of large transport aircraft and the 1% rule.

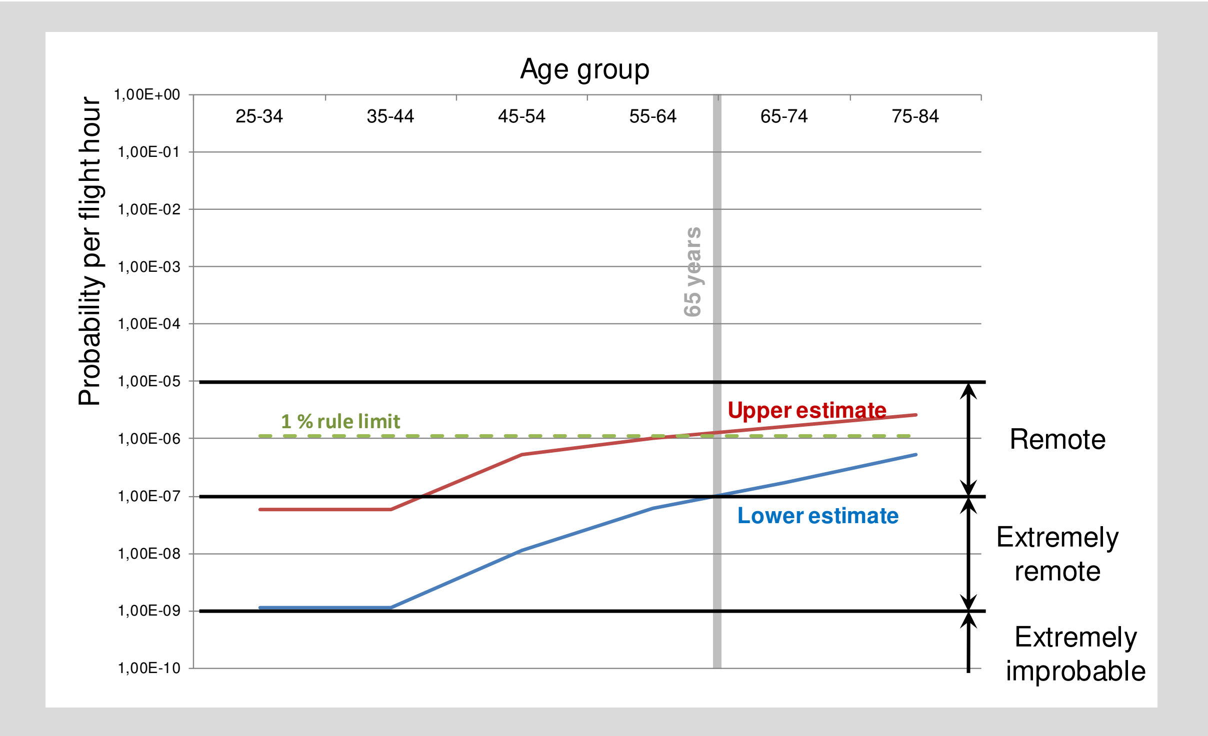

Figure 5.1 Estimated pilot incapacitation probability compared with CAT system failure severity thresholds

Figure 5.1 shows that the lower and upper estimate of the probability of sudden complete pilot incapacitation fall in the ‘extremely remote’ and ‘remote’ range of likelihoods.

5.2 Single pilot operation

Current aviation certification specifications for small aircraft do not prescribe pilot incapacitation probability limits. A comparison with aircraft system safety requirements, as defined in CS 23.2510 is made

to derive plausible limits for pilot incapacitation. In single pilot operations, sudden and complete pilot incapacitation will be a catastrophic event. The allowable probability of a catastrophic system failure condition of a small aircraft ranges from 1×10^{-9} to 1×10^{-6} and depends on the airworthiness level of the aircraft (which is a function of the seating capacity) and the aircraft complexity.
Figure 5.2 presents the estimated pilot incapacitation probabilities as a function of age in relation to small aircraft probability thresholds for catastrophic system failures.

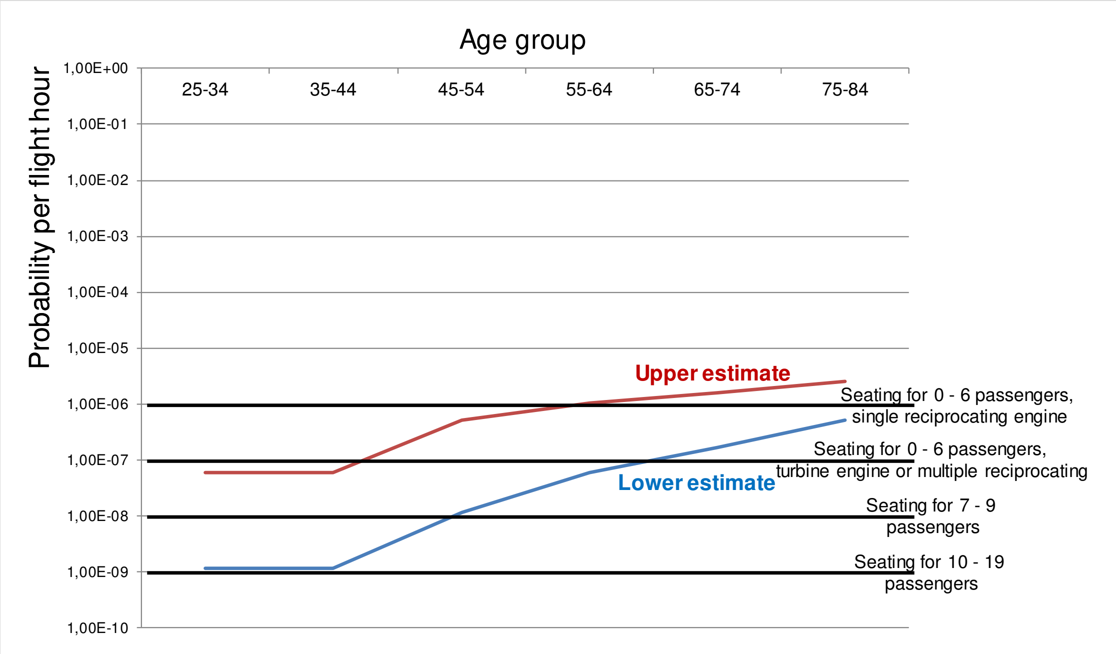

Figure 5.2 Estimated pilot incapacitation probability compared with small aircraft severity thresholds for catastrophic failures

6 Discussion and Conclusions

This study provides estimates of upper and lower boundaries of the rate of sudden in-flight incapacitation as a function of age. These estimates are based on general population mortality and hospital admission rates for cardiovascular events. The study was limited by a lack of information on reported in-flight incapacitation events. The data in the European Central Repository for accident and incident reports in aviation are of poor quality. The cause of incapacitation, crew member involved and age of the incapacitated person are often not recorded.
The upper and lower estimates presented in Figure 5.1 only relate to age-dependent medical causes of incapacitation. Medical causes of incapacitation that are not age-dependent are not included. In Figure 6.1 the upper and lower estimates are compared with overall incapacitation rates based on incident data as presented by DeJohn et al. (2004) and IATA (2018). An average pilot age of 52[3] is assumed to be associated with the incapacitation rate. Note that these incident data derived point estimate, indicated by the star symbol in Figure 6.1, which includes all types of incapacitation (age related and non-age related) falls between the upper and lower estimates, thus providing some confidence regarding the representativeness of the estimates. In Figure 6.1, the upper and lower estimates are also compared with the overall incapacitation rate as a function of age estimated by Evans and Radcliffe (2012). This estimate (indicated by the dotted line in Figure 6.1), which includes all types of incapacitation (age related and non-age related), is higher than the upper estimate for the younger age groups, but closely matches the upper estimates for the age of approximately 50 onwards. This result indicates that for the higher age groups, the age-dependent incapacitation types are dominant, and provides further confidence with respect to the representativeness of the estimates, particularly for the older age groups.

Figure 5.1 shows that the lower and upper estimates of the probability of sudden complete age-related pilot incapacitation fall in the ‘extremely remote’ and ‘remote’ range of likelihoods, as defined by EASA CS 25 for aircraft system failures. Considering that the effect of sudden and complete incapacitation of a pilot in a two pilot crew can be considered a major condition (see Section 2), the associated probability of occurrence must be remote. The estimated incapacitation rate meets this requirement for all age groups up to and including the 75-84 age group. In Figure 5.1 the ‘1% rule’ limit is also shown. This rule specifies a predicted annual medical incapacitation rate which, if exceeded, would exclude a pilot from flying in a multi-crew aircraft. This is widely regarded as an acceptable risk level and was adopted by the European Joint Aviation Authorities as the basis of aeromedical risk assessment (ICAO, 2012). The upper estimate of the probability of sudden complete age-related pilot incapacitation crosses the 1% rule limit at the 55-65 age group. According to ICAO (2012), the ‘1% rule’ is only one of several means of defining regulatory cut-off points. The rule has been reviewed comprehensively, and some Contracting States have found a two per cent cut-off point to be justified. The upper estimate of the probability of sudden complete age-related pilot incapacitation crosses the 2% line, which corresponds with a probability of 2.28×10^{-6} per hour, around the age of 80.
According to Regulation (EU) No 1178/2011, the current age limitation for multi pilot CAT operations is the age of 65. The results presented in Figure 6.1 suggest that allowing pilots older than 65 in multi pilot CAT operations would probably require additional risk-mitigation measures such as specific tests to support aero-medical decision on the applicant’s fitness on an individual basis.

3 This was the average age of UK ATPL (aircraft) license holders in 2016 (CAA, 2017), and it is assumed that this is representative for worldwide commercial aviation.

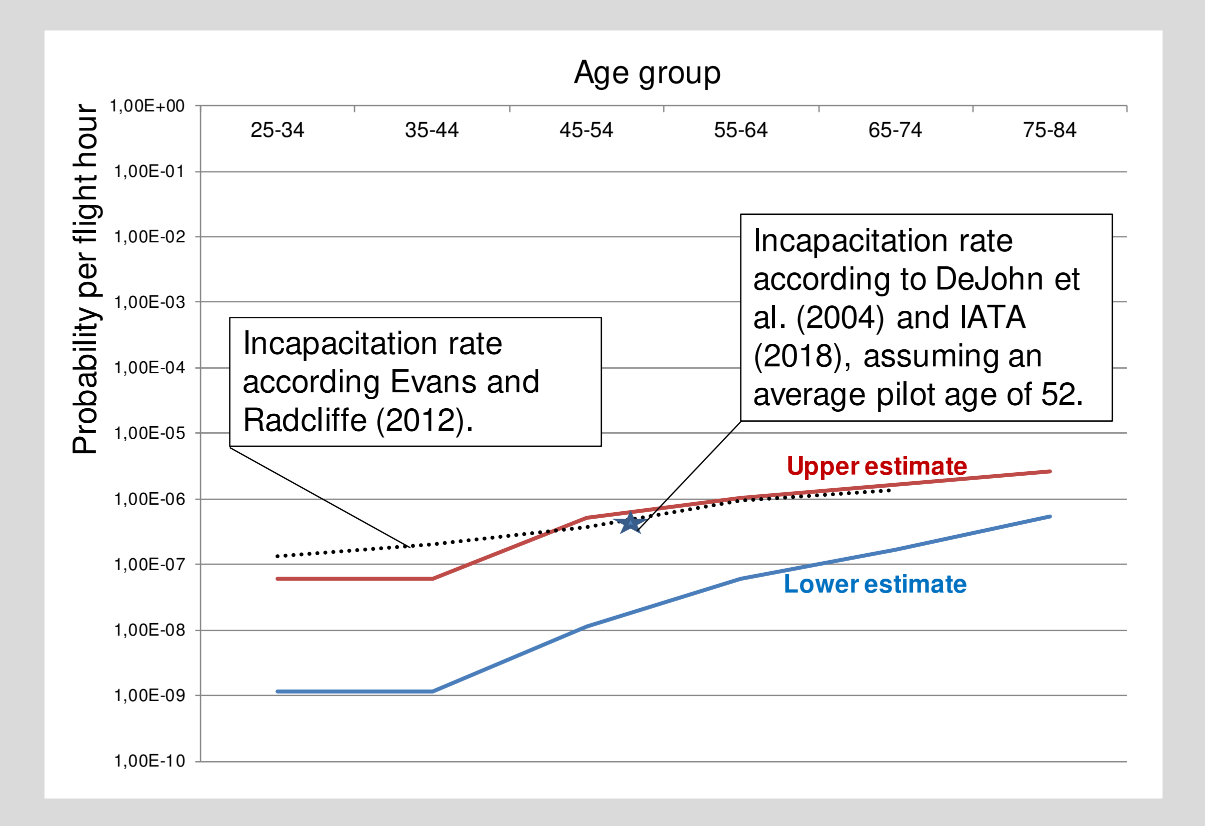

Figure 6.1 Estimated pilot incapacitation probability compared with incapacitation rates from incident data as presented in literature

Small CS 23 aircraft may generally be type certificated for single pilot operations, as long as demonstrations show the workload is acceptable (Faber, 2013). For single pilot operations sudden complete pilot incapacitation is a catastrophic event. Figure 5.2 shows that the upper estimate of sudden complete incapacitation crosses the acceptability limit for catastrophic system failures for CS 23 aircraft with a single reciprocating engine and a seating capacity for 0-6 passengers at the 55-64 age group. The upper estimate crosses the acceptability limit for catastrophic system failures for CS-23 aircraft with multiple reciprocating engines or a single turbine engine and a seating capacity for 0-6 passengers at the 35-44 age group. The lower estimate of sudden complete incapacitation crosses the acceptability limit for catastrophic system failures for CS 23 aircraft failures for aircraft with multiple reciprocating engines or a single turbine engine and a seating capacity for 0-6 passengers around the age of 65, and crosses the acceptability limit for catastrophic system failures for aircraft with a seating capacity for 7-9 passengers at the 45-54 age group. According to Regulation (EU) No 1178/2011, the current age limitation for single pilot CAT operations is the age of 60.
Figure 5.2 shows that for the more complex categories of CS 23 aircraft, the estimated probability of sudden complete incapacitation for pilots older than 60 does not meet the probability requirements that are defined in CS 23 for aircraft system failures. While a pilot is not an aircraft system and the system failure requirements are not applicable to pilot incapacitation, the system failure thresholds reflect acceptability of catastrophic accidents and therefore the comparison can be useful. The results suggest that any increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet current accident acceptability values. The results also suggest that for single pilots operations of complex aircraft the incapacitation risk is

relatively high. Specific tests to support aero-medical decision on the applicant's fitness on an individual basis for all age groups are perhaps needed to reduce the accident risk.

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Part 3 Screening of Cardiovascular Risks in Asymptomatic Pilots (Deliverable No. 3)

Project:	Age Limitations Commercial Air Transport Pilots
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Status:	Draft Final
Date:	08-01-2019
Author(s):	R. Simons, R. Maire, A. van Drongelen, P. Valk

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Content Part 3

1 Introduction

In Task 1 it was concluded that the most frequent age-dependent causes of sudden incapacitation include sudden death, acute coronary syndrome, cardiac arrhythmias, pulmonary embolism, transient ischemic attack (TIA), stroke (cerebral ischemic infarction, and cerebral haemorrhage), syncope, late-onset seizure(s), and acute psychosis.
In Task 2 risk assessment based on operational considerations showed that

1. Allowing pilots older than 65 years in multi pilot CAT operations would probably require additional risk-mitigation measures such as specific tests to support the aeromedical decision on the applicant's fitness on an individual basis; and
2. The risk of the 55-64 age group is just within the margin of the acceptability limit for catastrophic system failures for single piloted CS 23 aircraft with a single reciprocating engine and a seating capacity for 0-6 passengers.

It was concluded that there is a compelling need to reduce the medical incapacitation risk of single flying CAT pilots in the 55-64 age range and any increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet current operational accident acceptability values.

The by far largest number of total incapacitations is attributed to cardiovascular diseases and it is therefore considered that prevention of cardiovascular events may offer the best opportunity to significantly reduce the in-flight medical incapacitation risk in older CAT aircrew members. Discussion of risk assessment of age-dependent cardiovascular diseases will therefore be the main subject of this report of Task 3, while risk assessment of syncope, late-onset seizure(s), and acute psychosis will be further discussed in Task 4. In addition, because the project's main focus is on the medical causes of total incapacitation, considerations concerning more gradual or subtle incapacitation, such as sensory and/or cognitive impairment, will only briefly be discussed in the report of Task 4.

Cardiovascular causes of total incapacitation

The group of cardiovascular diseases and events that will be discussed in the present report include sudden death, coronary artery disease, cardiac arrhythmias, pulmonary embolism, and stroke (cerebral ischemic infarction, cerebrovascular accident, and cerebral haemorrhage).
Although it is known that atherosclerosis already starts to develop in early adulthood, or even childhood (Hong, 2010) the symptoms and life-threatening manifestations of cardiovascular disease (CVD) start to emerge at middle age, especially in those over the age of 40, which is demonstrated by an at least 3-fold increase of all cardiovascular diseases (CVD) and myocardial infarction mortality in those over 40 years (AHA, 2018) and a 5-fold increase of new stroke cases in the 45-54 age group as compared with the under 45 age groups (Finegold et al., 2013; Buddeke et al., 2017).
Based on this reasoning and in agreement with the recommendation of the NATO HFM-251 Occupational Cardiology in Military Aircrew working group (Gray et al., 2019) it is assumed that a thorough CVD risk assessment in CAT pilots from the age of 40 onwards will further reduce the risk of total in-flight incapacitation and will at the same time contribute to individual prevention of CVD.
In a clinical setting it is generally accepted to use risk stratification for appropriately allocating preventive treatment, which ranges from lifestyle measures, low- to high-intensity medical therapy (e.g., statin) to coronary artery revascularization (Piepoli et al., 2016; Arbab-Zadeh & Fuster, 2016). It is considered that a similar approach will be equally successful to assess risk in the context of pilot screening in order to prevent in-flight incapacitations due to cardiovascular events. Analogous to the clinical preventive approach, in the first stage of risk stratification, CVD risk estimation tools can be used to complement the medical examination. If this first-stage risk estimation indicates an intermediate or higher risk level, a broader cardiological risk assessment will be needed using enhanced diagnostic methods. This pro-

cedure is in agreement with the recent recommendations of the NATO Aviation Working Group (https://heart.bmj.com/content/heartjnl/105/Suppl_1/s17.full.pdf and - Gray et al., 2019).
In the context of compulsory aeromedical examinations the stratified cardiovascular risk estimation tools should

1. Have a sound scientific basis;
2. Include considerations about its decision criteria;
3. Be practical; and
4. Be cost efficient.

In addition, in the first stage of stratified risk assessment, the diagnostic criteria should be able to identify pilots at low, intermediate, and high risk. The classical cardiovascular risk factors hypertension, obesity, diabetes mellitus, hypercholesterolemia, positive family history, sex, smoking and age form the basic parameters for the calculation of the cardiovascular risk. Cardiovascular disease is caused by the interaction of a number of risk factors over years and the relevant cardiovascular burden is given by the severity and amount of all classical cardiovascular risk factors. In this interaction, the role of increasing age is complex. E.g., risk factors such as blood pressure, cholesterol, and diabetes type 2 often increase when age increases, while the effect of cellular senescence per se is less clear (McHugh & Gil, 2018).

2 Method

In this report the use of simple risk estimation tools will first be discussed (Section 3), followed by enhanced cardiological risk determination methods to be used in the second stage of the stratified risk assessment (Section 4). Validity, reliability, predictive capacities, potential limitations of the available cardiovascular risk assessment tools to be used in the initial and enhanced diagnostic stages of stratified risk assessment were evaluated based on analyses of relevant literature collected through an extensive Medline search strategy. Search terms used were: cardiovascular risk factors, coronary artery disease risk assessment, cardiovascular risk estimation; cardiovascular risk prediction; cardiovascular risk stratification; cardiovascular risk calculator, coronary artery calcium score, CT coronary angiogram, exercise testing, vascular ultrasound imaging, initial cardiovascular risk screening, enhanced cardiovascular risk screening, aeromedical screening.
Cost-effectiveness, practicality and accessibility for users, and optimal periodicity of the recommended tests will be further discussed in the report of Task 4. In Section 5, the recommendations and conclusions concerning the proposed optimal stratified cardiovascular risk assessment of CAT pilots are presented.

3 Risk Estimation Tools for Risk Assessment of CVD in European CAT Pilots

3.1 Medical history and general examination

A comprehensive risk assessment should include a full clinical history and should cover modifiable and non-modifiable risk factors to be considered in making a clinical judgement about the individual's medical and mental incapacitation risk. Systematic cardiovascular risk assessment is a most important part of the aeromedical screening and is recommended in individuals at increased CVD risk, i.e. with family history of premature CVD, familial hyperlipidaemia, major CV risk factors (such as smoking, high BP, DM or raised lipid levels) or comorbidities increasing CV risk (e.g., chronic kidney disease).
Pilots who are found to be at very high or high risk based on documented cardiovascular disease, diabetes mellitus (>40 years of age), kidney disease or highly elevated single risk factor (e.g., cholesterol >8 mmol/L in familial hypercholesterolaemia or very high blood pressure, e.g., BP ≥180/110 mmHg) should be referred for further expert cardiological evaluation (Piepoli et al., 2016).

In accordance with the 2016 European Guidelines on cardiovascular disease prevention in clinical practice (Piepoli et al., 2016), it is recommended to do a total CVD risk estimation, using a risk estimation tool (see Section 3.2), for all pilots >40 years of age who do not have one of the afore-mentioned high risk conditions.

3.2 CVD risk estimation tools: 'risk calculators'

Using risk estimation tools as part of a full aeromedical examination is considered to contribute significantly to the evaluation of the individual CVD risk. Using the levels of certain risk factors, the CVD risk estimation tools enable the assessment of an individual's risk for the development of cardiovascular events such as sudden heart death, myocardial infarction, and fatal or non-fatal stroke. A risk estimation tool is constructed as an equation with a regression coefficient for each included risk factor, based on a statistical analysis of data from a population of a certain region (the 'derivation cohort'). The derived regression equation is in most cases further transformed into a score, chart, graphic, or used for a computer program. Estimation tools may differ in their outcome in that some tools only predict CVD mortality (fatal outcomes), while others predict mortality as well as morbidity (fatal + non-fatal outcomes). Non-fatal events such as acute coronary syndromes, or stroke as well as fatal cardiac events have significant aeromedical consequences, and therefore, it is recommended to use a risk calculator that includes both non-fatal and fatal endpoints.
Presently, there are more than 100 different risk estimation tools available worldwide. The majority of risk estimation tools is based on the conventional risk factors such as age, gender, smoking, blood pressure, and cholesterol. Some tools include additional risk factors such as diabetes mellitus (DM), family history of CVD, and differentiate the lipids (listing LDL-cholesterol, HDL-cholesterol, triglycerides). The decision as to which risk calculator is most appropriate should be based on specific factors of the population being screened and should include consideration for age, ethnicity and gender. It should be considered that most existing cardiovascular risk prediction estimation systems for use in apparently healthy persons have been developed from cohort data that were collected 20 to 30 years ago. Because since then mortality and morbidity rates for cardiovascular diseases have improved in Europe and the US, some currently available prediction models tend to overestimate the risk of cardiovascular disease (Damen et al., 2018).

It is considered that all risk estimation tools are primarily developed for primary (or in some cases secondary) prevention of CVD and there is no risk estimation tool developed to predict the specific CVD-incapacitation risk of pilots. However, because the outcome of the 'preventive' risk estimation tools can be considered to be 1:1 applicable for the CVD-incapacitation risk of pilots, the most frequently used CVD risk estimation tools will be discussed in the underlying report and recommendations will be made concerning the tools that are most useful for stratified CVD risk assessment of commercial pilots.
The applicability of these instruments depends on the derivation cohorts, risk factors and endpoints that are considered, applied statistical methods, and formats used. The performance of a tool can be assessed over risk estimation on the derivation cohort (internal validation) or on another population (external validation).
For many years, the Framingham cardiovascular risk equation (Table 1) has been the preferred method of cardiovascular risk assessment. However, in February 2010, the National Institute for Health and Clinical Excellence (NICE, 2014) announced that the Framingham equation should be considered as just one of several acceptable methods. The same guideline included a systematic review, which found 110 different cardiovascular risk scoring methods. Clinicians are now able and expected to select, from these 110 cardiovascular risk scores, one that is appropriate for their patients. When using one of these tools, one must be familiar with the background on which the score relies (i.e. derivation cohort, sample size, internal and external validation), and one must know the Pros and Cons of the score, because there are many disparities within the different score systems. Many risk CVD estimation tools have not been externally validated or directly compared on their relative predictive performance, making them currently of unknown value for practitioners, policy makers, and guideline developers (Damen et al., 2016). Comparing the relative risk increases for consistent risk factor changes across 16 different cardiovascular risk calculators, Allan et al. (2015) found that cardiovascular risk calculators weigh the same risk factors differently. For each risk factor, the relative risk increase from the calculator with the highest increase was generally three to eight times greater than the relative risk increase from the calculator with lowest increase.
In the context of the present project a selection of most frequently used or recommended risk estimation tools will be discussed (Table 1). Risk estimation tools were selected using the following criteria:

- The tool should be made for primary prevention of CVD potentially relevant for European (EU) populations. This means that the derivation cohort of the risk tool should be representative for several European countries or the the risk tool was externally validated using EU cohorts;
- In analogy with Gorenoi and Hagen (2015) only risk estimation tools were considered which were derived from cohorts of at least 1,000 participants of one gender without pre-existing CVD, enable risk assessment for a period of at least 5 years, were designed for an age-range of at least 25 years and published after the year 2000;
- Tools should be included in clinical guidelines for therapeutic management and recommended by well-renowned health policymakers, such as NCEP (National Cholesterol Education Program), American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA), National Institute for Health and Clinical Excellence (NICE), European Guidelines on CVD Prevention (Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice), JBS3 Guidelines (Joint British Societies; Board, 2014), and International Task Force for Prevention of Coronary Disease Guidelines;

The risk calculator should be accessible online.

Table 3.1 Selection of the most frequently used risk estimation tools in Europe and United States

	Framingham	SCORE	PROCAM/AGLA	QRISK1, QRISK2, QRISK3	Pooled Cohort Equations	Reynolds Risk Score
Key Reference	D'Agostino et al., 2008	Conroy et al., 2003	Assmann et al., 2002; 2007	Hippisley-Cox et al., 2008; 2010; 2017	Goff et al., 2014	Ridker et al., 2008
Derivation Cohort	General population, Framingham, Massachusetts, USA. Baselines: 1968–71, 1971–75, 1984–87	12 prospective studies from 11 European countries. Baselines: 1972–1991	Germany: Healthy employees. Baseline: 1978–1995	UK: Data collected from 1993–2008 from GP databases – imputation of missing data	Baselines 1987–89 (ARIC), 1990 and 1992–3 (CHS), 1985–6 (CARDIA), 1968–71, 1971–75, 1984–87 (Framingham)	US Women: Health Service employees-baseline 1993-1996 US Men: Physicians-baseline 1997 Volunteers - not random
Sample Size	3969 men and 4522 women	117 098 men and 88 080 women	18 460 men and 8515 women	1.28 million (QRISK1) 2.29 million (QRISK2)	11 240 US white women, 9098 US white men, 2641 Afro-American Women, 1647 Afro-American men	24,558 women and 10,724 men
Calculates:	Latest version: 10-year risk of CVD events NCEP ATP III version: 10-year risk of hard coronary events	10-year risk of fatal CVD events	Two separate scores: 10-year risks of major coronary events and cerebral ischaemic events	10-year risk of CVD events. Lifetime risk	10-year risk for a first atherosclerotic CVD event. Lifetime risk	10-year risk of myocardial infarction, stroke, coronary revascularization, or cardiovascular death
Age Range(yrs)	30–75	40–65	20–75	35–74	20–79	45–80 years
Variables	Sex, age, total cholesterol, HDL-C, SBP, smoking status, DM, antihypertensive treatment	Sex, age, total cholesterol or total cholesterol/ HDL-C ratio, SBP, smoking status. Versions for use in high and low-risk countries	Age, sex, LDL-C, HDL-C, DM, smoking, SBP	Age, sex, total cholesterol/HDL-C ratio, SBP, smoking status, DM, area based index of deprivation, family history, BMI, antihypertensive treatment, ethnicity and chronic diseases	Age, sex, race (white or other/African American), total cholesterol, HDL-C, SBP, anti-hypertensive treatment, DM, smoking	Sex, age, SBP, smoking, hs-CRP, total cholesterol, HDL cholesterol, family history of premature MI (parent <60 years),

	Framingham	SCORE	PROCAM/AGLA	QRISK1, QRISK2, QRISK3	Pooled Cohort Equations	Reynolds Risk Score
Risk Levels	Low <10% Intermed. 10-20% High >20%	Low 0-4% Intermed. 5-9% High ≥ 10%	Low <10% Intermed. 10-20% High >20%	High >10%	Elevated risk ≥ 7.5%.	Low <10% Elevated/increased >10%
External validation in EU cohorts?	Yes	Yes	Yes	No but extensively validated and recalibrated in UK	No	No
Recommended by guidelines	NCEP guidelines Canadian CV guidelines Other national guidelines: adapted versions	European Guidelines on CVD Prevention	International Task Force for Prevention of Coronary Disease Guidelines	NICE guidelines on lipid modification. JBS3 guidelines	2013 AHA ACC Guideline on the assessment of CVD risk	NATO Cardiology Working Group: “possibly appropriate”

A perfect discrimination, shown by an Area Under the Receiver Operating Characteristic curve (AUROC) value of 1.0, of a risk estimation tool for CVD is not possible. Even the internal validation for various tools did not achieve the AUROC value of 0.9. The AUROC value of 0.75 was proposed as the minimum requirement for a risk estimation tool to be applied (Grover & Lowensteyn, 2011), and all risk calculator tools mentioned in Table 1 attain this value (Gorenoi & Hagen, 2015). As more risk factors are included in the model, such as is the case in The Astronaut Cardiovascular Health and Risk Modification (Astro-CHARM; Khera et al., 2018), the system becomes more complex, time consuming, and costly because a greater number of risk factors have to be measured to estimate the risk. This increase in complexity can impact the usage of the system (Cooney et al., 2009).
Users of risk calculators should realize that difficulties may arise when one is not informed about the basic characteristics of the risk estimation tool (e.g., representative derivation cohort) and the cut-off values that are used to discriminate between the different risk factor categories (low, intermediate, high). Risk factor levels that lie on the boundaries between two risk factor categories may lead to miscalculations of the risk category. Due to non-additive interactions that exist between coronary risk factors, the coronary risk curve rises much more steeply at high levels of risk than at low levels (International Task Force for Prevention of Coronary Heart Disease, 2003).
In the discussion of risk estimation for a broad European cohort of CAT pilots, risk estimation tools that used prognostic variables that are only based on data of specific national derivation cohorts will not be discussed. The CUORE risk estimation tool (Giampaoli et al., 2007) and the ASSIGN-SCORE (Woodward et al., 2007) are tools that are based on data of a specific national derivation cohort (Italy and Scotland respectively). The ASSIGN-SCORE considers social deprivation as risk factor using the Scottish Index of Multiple Deprivation (SIMD) score. Both CUORE and ASSIGN have not been evaluated using external validation. Due to the potential differences in genetics, lifestyle, and environment, these risk estimation tools will not be discussed on the context of risk assessment of European CAT pilots. Although the Reynolds Risk Score (RSS, Table 1) is also based on a specific national derivation cohort (US physicians), the RSS will be discussed in the underlying report because this risk calculator was recently recommended for the cardiovascular screening of military NATO aircrew (Gray et al., 2019).

Framingham risk score (D'Agostino et al., 2008)
The Framingham risk score is a multivariable risk function that predicts 10-year risk of developing cardiovascular disease events (coronary heart disease, stroke, peripheral artery disease or heart failure). The sex-specific scores incorporate age, total and high density lipoprotein cholesterol, systolic blood pressure, treatment for hypertension, smoking, and diabetic status. A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of cardiovascular events. This tool is intended for use among patients aged 30-79 years with no prior history of coronary heart disease.

The Framingham data, while thorough, come from many years ago (1968-1987) with a potentially different US population along with a different diet and level of smoking as well, which may suggest different risk levels today. This might be one of the reasons that the Framingham is considered to overestimate the risk in a 21-century-society (e.g. Hense et al., 2003; Sing, 2004).
The Framingham Risk Score (Table 1) is used in health economic analyses to predict the risk for future coronary heart disease events. However, based on an American population, the Framingham Risk Score has been criticized for potential overestimation of cardiovascular risk in European populations. Only three studies have validated the use of the Framingham Risk Score in health economic studies modelling the effects of lipid lowering treatment on coronary heart disease events in European populations. Those studies reported an overall satisfactory accuracy in the risk predictions by the Framingham Risk Score, but the risk for non-fatal myocardial infarctions tended to be underestimated (Hermansson & Kahan, 2018). The Framingham risk model performed reasonably well in Indian men, but overesti-

mated risk in Indian women and in Europeans (Rabanal et al., 2018). Framingham online risk calculator is available at: https://www.mdcalc.com/framingham-coronary-heart-disease-risk-score.

SCORE (Conroy et al., 2003)
The Systematic Coronary Risk Evaluation (SCORE) risk charts are the most widely used of the risk scoring tools, as they are recommended by the European Society of Cardiology (ESC; Piepoli et al., 2016) and cardiology societies from several European countries. The SCORE algorithm was derived from a pooled data set of CVD mortality of more than 200,000 individuals aged 19-80 years from 12 European cohort studies that represented 11 countries, giving it the advantage of including a broad range of patient populations. Using derived equations the charts for risk of fatal CVD within 10 years were constructed separately for countries with a high or low CVD-risk based on cardiovascular death rates and age-standardized death rates in national mortality statistics. Even with this adjustment for regional variability, further calibration of the SCORE charts was required for several countries, including Belgium, Germany, Greece, The Netherlands, Poland, Spain and Sweden; this is reflected in the recent version of the ESC guidelines (Graham et al., 2007). SCORE has been applied to Spanish and Dutch populations and showed a very good discrimination (Gorenoi et al., 2009).
Published SCORE risk charts incorporate the conventional variables age, systolic blood pressure, total cholesterol (or total cholesterol/ HDL-C ratio), gender and smoking status and enable risk estimation for persons aged 40-65 years of each region. The SCORE charts presented on the website (example: https://heartscore.escardio.org/2012/calc.aspx?model=europelow) are based on age, gender, total cholesterol, HDL-cholesterol, Systolic Blood Pressure (SBP), and smoking and offer also relative risk estimation.
The SCORE predicts 10-year risk on **fatal** cardiovascular disease. A score of 0-4% is considered low, 5-9% intermediate, and ≥10% high risk of cardiovascular death in 10 years.
Advantages of the SCORE risk charts are that it is an intuitive, easy to use tool and that it is adapted to suit different European populations. The risk of coronary heart disease and stroke death can be derived separately.

Limitations in using the SCORE risk charts for risk assessment in EU CAT pilots are that it estimates risk of fatal but not total (fatal + non-fatal) CVD risk, while a non-fatal cardiac event might well be one of the causes of in-flight incapacitation. Other limitations are that the age range is limited to 40-65 years and that it is limited to the major determinants of risk. It is based on data of rather old cohorts (1972-1991) which may lead to overestimation of the risk in modern cohorts. Because background risk for fatal CVD differs across Europe, the 2003 ESC guidelines provided two standard versions of SCORE that are still used for risk assessment (Piepoli et al., 2016): one for countries with low cardiovascular mortality (low-risk SCORE version), the other for countries with high cardiovascular mortality (high-risk SCORE version). Because of declining CVD mortality, many more European countries are now classified as low-risk countries (*n* = 24) than in 2003 (*n* = 8), and even the low-risk SCORE version overestimates 10-year risk for fatal CVD in several of these countries today (Mortensen & Falk, 2017). SCORE has been recalibrated in many countries across Europe based on national cause specific mortality rates. Since these national CVD mortality rates include everyone, also high-risk patients who do not qualify for SCORE-based risk assessment (patients with known CVD, diabetes, familial hypercholesterolemia, kidney disease or statin use), this recalibration method will most likely lead to overestimation of risk in the healthy subpopulation where SCORE is going to be used (Mortensen & Falk, 2017).

QRISK1, 2, and 3 (Hippisley-Cox et al., 2008; Hippisley-Cox et al., 2010; Hippisley-Cox et al., 2017)
The QRISK 1 and 2 and 3 risk scores (Table 1) developed in Great Britain and recommended by the UK National Institute for Health and Care Excellence (NICE) showed a relatively good discrimination for primary care patients in Scotland and Northern Ireland. QRISK2, the successor to QRISK1, allows to

predict risk more accurately among people from different ethnic groups. Risk factors incorporated in the QRISK2 CVD risk calculator are age (25-84), sex, ethnicity, UK postal code, smoking, diabetes, family CVD in a 1st degree relative < 60, chronic kidney disease, atrial fibrillation, antihypertensive treatment, rheumatoid arthritis, Cholesterol/HDL ratio, systolic blood pressure, and body mass index.
The online QRISK2 calculator is available at: https://qrisk.org/2016/. It provides the following outcomes:
- A 10-year QRISK2 score;
- The score of a healthy person with the same age, sex, and ethnicity;
- Relative risk compared with a healthy person with the same age, sex, and ethnicity;
- Your QRISK® Healthy Heart Age.

QRISK2 has been updated into QRISK3 and these risk prediction algorithms have recently been validated and updated to estimate the 10 year risk of cardiovascular disease in women and men accounting for potential new risk factors (Hippisley-Cox et al., 2017). It was found that the inclusion of additional clinical variables in QRISK3 (chronic kidney disease, a measure of systolic blood pressure variability (standard deviation of repeated measures), migraine, corticosteroids, SLE, atypical antipsychotics, severe mental illness, and erectile dysfunction) can help enable doctors to identify those most at risk of heart disease and stroke.
The risk estimation stands out best when the socio-economic environment of the patient is taken into account and therefore one of the variables is the UK postal code. The postal code is used to include socio-economic influences in the model, which is useful but specifically tied to the social characteristics of a concerning area in UK (Hippisley-Cox et al., 2008; Hippisley-Cox et al., 2010). However, the risk score can also be used by omitting the postal code. The QRISK2 and 3 incorporate the largest number of traditional and additional variables of all risk estimation tools discussed in this report. The QRISK system is primarily developed to predict CVD risk in England and Wales and is externally validated using independent British cohorts. The performance of QRISK2 and 3 in cohorts of other European nations is unclear.

PROCAM (Assmann et al., 2002) Prospective Cardiovascular Munster Study
The German PROCAM score can be referred to as the first internationally known European risk estimation tool. The first version was developed as a point score for estimating the risk of a coronary event within 10 years and was published in 2002 (Assmann et al., 2002). The new version of the PROCAM score, released in 2007, is based on the data from 27,000 employees aged 20-78 years, of which one third were female (Assmann et al., 2007). Therefore this new version allows risks estimations for female and a broad age range.
Beyond conventional risk factors data on age, LDL- and HDL-Cholesterol and Triglycerides, DM and a family history of MI (<55 years males; <65 years females) were used as prognostic variables. PROCAM participants were followed up for acute coronary events (myocardial infarction, sudden cardiac death) for 10 years. A score below 10% is considered low, 10%-20% intermediate, and >20% high 10-year risk of coronary events (fatal + non-fatal).
An online version of the most recent PROCAM risk calculator is provided on http://www.kardiolab.ch/MONICA-PROCAM3_RA1.html and calculates the relative risk of a coronary event (age range of this version is up to 65 years). The new version of the PROCAM score also presents a point score for the risk of an ischemic cerebral event within 10 years (Assmann et al., 2007). This score was derived from the data of about 8,000 participants aged 35-65 years of the entire PROCAM cohort and based only on the risk factors gender, age, smoking, blood pressure, and diabetes mellitus. Using epidemiological corrections by regional adjustment factors based on data from the MONICA project (https://cordis.europa.eu/result/rcn/23509_en.html), PROCAM algorithms can be adapted for use in many European countries thereby estimating CVD risk of a derivation cohort that is representative for the nationality in question (http://www.kardiolab.ch/MONICA-PROCAM3_RA1.html).

The Swiss Atherosclerosis Association (www.agla.ch/) uses such country-specific adapted version of the PROCAM algorithm (AGLA) with a regional adjustment factor of 0.7 for Switzerland and an age range up to 75 years. This version is used in the stratified CVD risk assessment of pilots in Switzerland. The AGLA risk calculator is online available: https://www.agla.ch/risikoberechnung/agla-risikorechner or https://www.gsla.ch/calcul-du-risque/calculateur-de-risque-du-gsla.

Pooled Cohort Equations (Goff et al., 2014; table X)
The peer-reviewed online calculator of the Pooled Cohort Equations was developed to estimate the 10-year primary risk of ASCVD (atherosclerotic cardiovascular disease) among patients without pre-existing cardiovascular disease who are between 40 and 79 years of age. Patients are considered to be at 'elevated' risk if the Pooled Cohort Equations predicted risk is ≥7.5%. In the US, the Pooled Cohort Equations have been proposed to replace the Framingham Risk 10-year CVD calculation, which was recommended for use in the NCEP ATP III guidelines for high blood cholesterol in adults. One of the advantages of this risk score for use in the US is that it is made also applicable for African-Americans. An early criticism of the Pooled Cohort Equations Risk Calculator has been its alleged overestimation of ASCVD risk which, if confirmed in the general population, is likely to result in statin therapy being prescribed to many individuals at lower risk than the intended 7.5% 10-year ASCVD risk threshold for treatment in the joint ACC/AHA cholesterol guidelines. Online Pooled Cohort Studies online risk calculator is available at: https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx.

Reynolds Risk Score (Ridker et al., 2008)
The development of the Reynolds Risk Score (RRS) was aimed to use several new risk factors associated with increased risk for CVD such as metabolism-related variables (e.g., lipoprotein A), inflammatory markers (C-reactive protein), markers of glucose metabolism, plasma creatinine and homocystein values. Primarily, several equations were published in 2007 to calculate the risk of a cardiovascular event based on the data of an occupational cohort of more than 16,000 U.S. women (Ridker et al., 2007). The simplified risk estimation equation (RRS) uses in addition to conventional risk factors and family history of MI (first line <60 years) the variable high sensitivity - C-reactive protein (hs-CRP). The RRS equation for men was published in 2008 and based on the data of an occupational cohort of almost 11,000 U.S. non-diabetic physicians (Ridker et al., 2008). The risk estimation tool has the same endpoint and uses the same risk factors compared to the published equations for women.
The website (www.reynoldsriskscore.com/) of the RRS enables to estimate the 10-year risk of a cardiovascular event at current age as well as at next age-decades for non-diabetic persons aged 45-80 years using conventional risk factors, family history of MI and the variable hs-CRP. Family history and hs-CRP ≥2.0 mg/L both appear to be significant markers of risk (Ridker et al., 2008) and therefore the RRS may be recommendable for the screening of aircrew (Gray et al., 2019). Gray et al. (2019) recommend the RRS in the context of screening NATO aircrew which for a large part includes US and Canadian pilots. It should, however, be considered that the RRS is based on a derivation cohort of US Physicians (not randomly recruited volunteers), and that external validation has not been assessed. Therefore, it is arguable whether the RRS is the optimal risk calculator for EU CAT pilots.

3.3 Other risk estimation methods

Exercise Stress Testing
There is insufficient scientific basis for Exercise Tolerance Testing in the stratified risk assessment of apparently healthy individuals. Exercise tolerance testing (also known as exercise stress testing) is used routinely in evaluating patients who present chest pain, in patients who have chest pain on exertion, and in patients with known ischemic heart disease (e.g., Hill & Timmis, 2002). Exercise stress testing is

useful to assess aerobic fitness, blood pressure response, and arrhythmias. Exercise stress tests do not have the required sensitivity required to suggest their use as part of a screening protocol in **asymptomatic** individuals (Shah et al., 2015). Therefore, the use of exercise stress testing in the initial screening of aircrew is not recommended. In some cases exercise stress testing may be indicated in an enhanced screening procedure (phase 2 of the stratified approach).

Resting Electrocardiogram

In the initial cardiovascular screening of aircrew a routine 12-lead resting ECG is recommended to identify abnormal conduction or other arrhythmogenic patterns that could increase the risk of cardiovascular incapacitation in aircrew such as left bundle branch block, WPW-syndrome, cardiomyopathies as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy or inherited diseases such as long or short QT syndromes and Brugada syndrome. However, a resting ECG is not a good discriminator for the prediction of acute coronary events in asymptomatic adults at low risk of cardiovascular events and should therefore not be used to predict the 5- or 10-year risk of coronary disease in asymptomatic aircrew.

Genetic Testing

Many commercial genetic tests are available and there is strong commercial pressure to use these tests to predict genetic risks and to make genetic testing a routine measure (Singleton et al., 2012). Several recent genome-wide association studies have identified candidate genes associated with CVD. Because the effect of each genetic polymorphism is small, most studies have used genetic scores to summarize the genetic component. There is no consensus regarding which genes and their corresponding single nucleotide polymorphisms should be included in a genetic risk score and which method should be used to calculate the genetic score. Most prospective studies of the association of genetic scores with incident CVD have found a significant association, with the relative risks varying between 1.02 and 1.49 per increase in one score unit (Sivapalaratnam et al., 2010).

Because there is no agreement concerning which genetic markers should be included, how genetic risk scores should be calculated and uncertainties about improvement in CV risk prediction, the use of genetic markers for the prediction of CVD is not recommended (Piepoli et al., 2016). A parental history of premature CVD is a well-established risk factor for incident CVD (Lloyd-Jones et al., 2004; Murabito et al., 2005) and a positive family history of premature CVD is considered to represent a good surrogate for an increased genetic risk (Ridker et al., 2008; Ridker et al., 2007; Murabito et al., 2005).

Biomarkers

High sensitivity C reactive protein (hs-CRP) is a widely investigated biomarker of inflammation and a level of ≥2.0 mg/L is considered a significant marker of cardiovascular risk (Ridker et al., 2008). A hs-CRP level <1.0 mg/L is associated with a low risk of CVD, a level between 1.0 mg/L and 3.0 mg/L means an intermediate to moderate risk, and a hs-CRP level of > 3.0 mg/L is associated with a high risk. There is evidence (level B: consistent results in randomized and non-randomized well designed controlled studies) that hs-CRP, is a significant predictor of cardiovascular risk in apparently healthy individuals, particularly in combination with total cholesterol and HDL-cholesterol (Mora et al., 2009). The American Heart Association (AHA) does not recommend an hs-CRP test for everyone, but states that the test is most useful if, after quantitative risk assessment a risk-based treatment decision is uncertain hs-CRP may be considered to inform treatment decision making (Goff et al., 2014). Family history and hs-CRP both appear to be significant markers of risk, and can be included in the overall estimated risk, if not included in the risk equation used.

It is evident that an increased serum apolipoprotein B (Apo B) concentration is an important coronary heart disease risk factor. Apo B is a component of all atherogenic or potentially atherogenic particles. Several authors claim the superiority of apo B measurement over that of LDL cholesterol for assessment of CVD risk (e.g., Contois et al., 2009). In their guidelines the AHA considers that that measurement of ApoB is of uncertain value and is therefore not yet recommended to include it in the risk assessment of a first CVD event (Goff et al., 2014). According to the AHA, hs-CRP and apolipoprotein B can be used as 'risk-enhancing factors' that are not considered in the risk calculator and, if present, 'might push one to go ahead and prescribe a statin, if the patient is agreeable'. Translated to the aeromedical screening of asymptomatic pilots, this would mean that an intermediate risk found with a risk calculator can be 'enhanced' to a higher risk level when C-reactive protein (high-sensitivity assay) is ≥2.0 mg/L or apolipoprotein B is ≥130 mg/dL.

3.4 Conclusion/recommendation initial screening

In Section 3.3 it was shown that, with exception of a 12-lead ECG, the majority of the other estimation tools are not appropriate for initial screening of asymptomatic pilots. We therefore recommend using a stratified cardiovascular risk assessment with CVD risk estimation tools (i.e. risk calculators) for the initial stage of CVD risk assessment in European CAT pilots. It is recommended to select a risk estimation tool that

1. Is based on a derivation cohort that is representative for the national health status or that is externally validated for the national cohort in question (e.g., for Germany use a German population derived risk calculation);
2. Uses the risk factors that are considered to be crucial;
3. Has been shown good discriminatory power; and
4. Predicts the risk for a relevant outcome (i.e. 5 or 10 year risk) and endpoint (i.e. fatal CVD, fatal + non-fatal CVD, stroke).

The advantages and limitations of the different risk calculators discussed are presented in Table 2.

Table 2 Advantages and limitations of most frequently used risk estimation tools in Europe and United States

	Framingham	SCORE	PROCAM/ AGLA	QRISK1, QRISK2, QRISK3	Pooled cohort equations	Reynolds Risk Score
Advantages	Externally validated in European population cohorts	Based on 12 EU cohort studies (11 countries) Recalibrated in many EU countries	Based on EU cohort and externally validated in many EU countries Algorithms can be adapted for use in different EU countries Also presents a point score for stroke risk	Good discrimination for primary care patients Accurate estimation for different ethnic groups Includes many risk factors	Based on large US database Also applicable for African-Americans	Risk factors include high sensitivity - C-reactive protein

	Framingham	SCORE	PROCAM/ AGLA	QRISK1, QRISK2, QRISK3	Pooled cohort equations	Reynolds Risk Score
Limitations	Based on US cohorts of 1968-1987: overestimation of risk	Estimates only fatal CVD risk Based on data of 1972-1991: risk overestimation Age range: 40-65 years	Older versions are still on internet. Only latest PROCAM version (2007) and AGLA have broad age range and also applies for females	Primarily developed to predict CVD risk in England and Wales Performance in cohorts of other EU nations unclear.	Alleged overestimation of risk Applicable to US population – not externally validated or recalibrated in EU cohorts	Based on US cohort of physicians Applicable to US cohorts – not externally validated or recalibrated in EU cohorts

In the context of screening European CAT pilots a 'European cohort-derived' estimation tool with 'hard' events such as myocardial infarction, stroke, or death (non-fatal + fatal CVD) as standardized endpoints is recommended. The Pooled Cohort Equations or Reynolds Risk Score may be recommendable for use in the US, but may be less representative for the EU health situation. The QRISK3 is recommendable for use in Great Britain but may also be less applicable for the continental EU countries.
Although the SCORE risk estimation system is based on broad EU derivation cohorts, it is considered less suitable in the context of risk assessment in EU CAT pilots, because its endpoint is only fatal CVD, while non-fatal CVD is also considered to be a significant determinant of medical incapacitation. Moreover, SCORE only uses total cholesterol for its risk score, while it is currently widely accepted that the level of LDL-cholesterol is the most important risk factor when considering the lipid metabolism.
The latest PROCAM algorithm uses data on age, gender, LDL- and HDL-cholesterol and triglycerides, systolic blood pressure, smoking, diabetes mellitus and a family history of myocardial infarction. For initial screening of European CAT pilots this version of the PROCAM algorithm appears to be an appropriate risk score system for CVD because the endpoints concern all CVD events (fatal + non-fatal) and the algorithm can be adapted for use in many European countries, thereby estimating CVD risk of a derivation cohort that is representative for the nationality in question
(see http://www.kardiolab.ch/MONICA-PROCAM3_RA1.html). The Swiss AGLA score is 'ready to use' in Switzerland because the reduction factor is already set for a Swiss cohort.
The variables gender and age alone are responsible for the AUROC of up to 0.7 (Cooney et al., 2009) and additional risk factor add only small values (0.01-0.1). Because the weight of age in the risk calculating algorithms is so prominent, it was tested whether the risk of pilots in the age group of 60-65 who had no traditional risk factors would be classified as low (<10%) using different risk calculators (Table 3). The table shows that there is no risk that older pilots who have no traditional CVD risk factors are classified in a higher risk category only based on their age. This observation shows that the risk is negligible that older pilots will have to be referred for enhanced cardiological screening based on age per se. Table 3 also shows that the risk calculated by the Framingham (FRS) and Reynolds calculators is higher than the SCORE or PROCAM scores. This observation might support the assumption that the FRS, and possibly the RRS, overestimates CVD risk in Europeans (Rabanal et al., 2018).

Table 3 10-years CVD Risk scores for males (60 to 65) without traditional risk factors calculated by different risk calculators (http://www.kardiolab.ch/MONICA-PROCAM3_RA1.html)

	Male 60 years % Risk/10 years	Male 65 years % Risk/10 years
Framingham Risk Score	4.30	5.56
SCORE (only fatal CVD)	1.29	1.89
PROCAM	1.53	2.55
Reynolds Risk score	3.00	4.00

All aircrew, especially those over the age of 40 years, should be periodically screened for cardiovascular risk using a resting ECG and risk estimating calculators that are representative and appropriate for the population to screen and include family history and provide non-fatal and fatal endpoints. This is in accordance with a current EASA requirement (MED.B.010 article 4) that for CAT pilots estimation of serum lipids, including cholesterol should be assessed at the first examination after having reached the age of 40 (EASA, 2011).
High sensitivity C reactive protein (hs-CRP) ≥2.0 mg/L and apolipoprotein B ≥130 mg/dL can be considered as risk-enhancing factors that are useful to be included in the overall estimated risk.
Systematic cardiovascular risk screening, including use of an appropriate risk score tool, will enable a reduction of in-flight incapacitation risk, which is in particular necessary when allowing an extension of the age limit for single flying CAT pilots to 65 years. The consequence of using an appropriate risk estimation tool is that in addition to the current aeromedical examination required by EASA, at least blood levels of LDL-cholesterol, HDL-cholesterol, and triglycerides (and preferably hs-CRP) are required to assess the CV risk. In addition, and in accordance with ICAO recommendations on prevention (Jordaan, 2017), it is also recommended to implement systematic CV risk screening for every aircrew member from the age of 40 onwards, in order to give individual advice on prevention of CVD through lifestyle management.

4 Enhanced Screening Methods

When the initial screening reveals an elevated or high CVD risk (e.g., >10% PROCAM risk score) or has a clinically determined higher risk of CVD, the pilot concerned should be referred to a cardiologist with aeromedical expertise for enhanced risk assessment in order to identify and substantiate the CVD risk and to advise on fitness for pilot duties and risk factor modification (individual prevention). Using risk calculation tools, the threshold for initiating enhanced screening of aircrew with increased risk for a coronary event is generally set at 10%. In the 2018-Guideline on the Management of Blood Cholesterol of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines (Grundy et al., 2018), it is considered that in cases with borderline low risk (5-10%) an enhanced screening method such as CT Coronary Artery Calcium Score might be used in order to evaluate whether primary prevention with statins should be started (Grundy et al., 2018).
Although the majority of cases of referral to cardiological expertise will concern coronary pathology (e.g., stenosis, plaques), it is emphasized that a cardiological examination is also indicated in cases of conduction abnormalities, arrhythmias, heart muscle disease, and valvular heart disease and aortopathy. In the context of the present report an overview of generally accepted enhanced screening methods to assess the functional coronary capacity and identification of ‘risky’ plaques will be given. It is considered that the cardiological diagnostic methods to be used in each specific case will be at the cardiologist’s discretion.
For aircrew identified as being at increased risk for a coronary event based on the initial risk prediction, use of one of the following generally accepted and frequently used methods is recommended:

- CT Coronary Artery Calcium Score (CACS);
- CT coronary angiogram (CTCA);
- Vascular Ultrasound Imaging (VUI).

4.1 CT Coronary Artery Calcium Score (CACS)

The determination of the coronary artery calcium by computed tomography, often called calcium scoring, is widely used. Its prognostic value has been well established by many publications (Baber et al., 2015; Budoff et al., 2013; Detrano et al., 2008). The CACS is a non-contrast, cardiac-gated CT that can be done in 10-15 minutes, with about 0.5 to 1 mSv of radiation (Einstein, 2015).
The determination of the CACS score by computed tomography is based on axial slices, with a thickness of 3 mm, without overlapping or gaps, limited to the cardiac region, acquired prospectively in synchrony with the electrocardiogram at a predetermined moment in the R-R interval, usually in the mid/late diastole, without the use of intravenous contrast medium. Calcification is identified as areas of hyperattenuation of at least 1 mm^2-with >130 Hounsfied units (HU) or ≥3 adjacent pixels. The main systems for the quantification of the CACS are the Agatston method, determination of the volume of calcium, and determination of the calcium mass score. The Agatston method is used as a reference for most population databases and publications involving risk stratification and is therefore the method most often used in clinical practice.
The Agatston method uses the weighted sum of lesions with a density above 130 HU, multiplying the area of calcium by a factor related to maximum plaque attenuation. Standardized categories for the calcium score have been developed with scores of 0 indicating the absence of calcified plaque, 1 to 10 minimal plaque, 11 to 100 mild plaque, 101 to 400 moderate plaque, and >400 severe plaque. Risk categories associated with the coronary calcium scores and their associations with the 10-year and annual coronary event rates are presented in Table 4.

Table 4 Interpretation of Calcium scores- Summary of CAC absolute event rates

CAC Score (CACS)	Risk	10-Year Event Rate % (Hecht, 2015) *n*=14,856	Annual Event Rate % (Rozanski et al., 2007) *n*=1,153
CACS = 0	Very low	1.1-1.7	0.45
CACS = 1-100	Low risk	2.3-5.9	1.11
CACS = 101-400	Intermediate risk	12.8-16.4	1.14
CACS > 400	High risk	22.5-28.6	3.00
CACS >1000	Very High	37.0	4.01

In the Heinz Nixdorf Recall Study, 4,487 subjects without CHD were followed for 5 years (Erbel et al., 2010). The prevalence of low (<100), intermediate (100-399), and high (≥400) CAC scores was 72.9%, 16.8%, and 10.3%, respectively.

CACS increases markedly with age by about 20-25% per year and about 20% of subjects with a CACS = 0 progress to CACS >0 in 5 years (Greenland et al., 2018). In the context of cost-effectiveness there might be a concern that a large number of older (60-65 years) aircrew will be found to have coronary calcium scores >100 which would consequently lead to a surplus of referrals for further cardiological examinations. Although data on the distribution of CACS by age cover different ethnic groups, a general estimation is that in the 55-64 age group around 50% of asymptomatic males have a CACS of 0 and around 35% have a CACS of 1-100, while in 13% the CACS is 101 to 300 and in around 11% the CACS is estimated to be over 300 (Greenland et al., 2018; Pletcher et al., 2013; McClelland et al.2006, Tota Maharaj et al. 2012). Based on these data it is assumed that around 15-20% of the 60-65 year aircrew might have to be grounded awaiting further cardiological examination. It is strongly recommended to keep records of all aircrew that is screened in order to evaluate the recommended stratified screening procedure. In asymptomatic patients, the absence of CAC predicts excellent survival with 10-year event rates of approximately 1%. Individuals with low CAC score (CAC 1-10) are at increased risk compared with individuals with CAC=0 (Blaha et al., 2009).

In a follow-up study (mean follow-up 14.6 years) of 9,715 individuals undergoing CAC imaging, Valenti et al. (2015) found that a CAC score of 0 gives a 15-year warranty period against mortality in individuals at low to intermediate risk that is unaffected by age or sex. In individuals with a CAC of 0, a repeat CACS may be considered in 4-5 years (Hecht, 2015). An annual increase in CACS of 15% or annual increase of CACS >100 units are predictive of future myocardial infarction and mortality (National Vascular Disease Prevention Alliance, 2012).

In the MESA study (Multi-Ethnic Study of Atherosclerosis), Criqui et al. (2014) found that CACS >0 had 99% sensitivity, 57% specificity, 24% positive predictive value, and 99% negative predictive value for acute coronary syndrome. In the same study cohort Detrano et al. (2008) found that the hazard ratio (HR) for a coronary event of those with a CACS of 101-300 was 7.7 compared with those who had a CACS score of 0. For those with a CACS >300 the HR was 9.7 (Detrano et al., 2008; Hecht, 2015). In a meta-analysis of 64,873 patients followed for 4.2 years the coronary event rate was 0.13% per year in individuals with a CAC score of 0 compared with 1% per year for those with a CAC score >0 (Sarwar et al., 2009).

A coronary calcium score of 100, at a population level, is an established clinical threshold above which the probability of obstructive disease and coronary events becomes moderately elevated, with event rates exceeding 1%/year (Greenland et al., 2010; Hecht, 2015). In conformity with this clinical threshold it is recommended that a CACS >100 should result in aircrew being temporarily grounded pending further investigation.

CACS is a strong predictor at population level but is in some cases a poor discriminator at individual level and if performed in isolation may not predict risk on an individual basis, mainly because CACS is not sensitive to identify non-calcified plaques (e.g., Parsons et al., 2017) and it is known that a large number of vulnerable plaques are predominantly non-calcified (Hausleiter et al., 2006). Cases with significant stenosis on Computed Tomography Coronary Angiography (CTCA) who had a CACS of 0 as well as cases with high CACS levels (>100) who had <50% stenosis on CTCA have been described (Nicol, 2018).

Calcium score is a robust predictor of coronary events and stroke in the asymptomatic primary prevention population and is incremental to risk factors (Shaw et al., 2003; Rana et al., 2012; Hecht, 2015). A combination of the CACS with clinical data, for example using the classical cardiovascular scores mentioned above, leads to a significant improvement of the CVD risk assessment and preventive treatment (Lloyd-Jones, 2015; McClelland et al., 2015). CACS has a proven ability to reclassify an initially found cardiovascular risk into lower or higher risk groups (Greenland et al., 2018). CACS is of most value in individuals with intermediate risk (absolute 10-year cardiovascular risk of 7.5-20%) (Grundy et al., 2018) who are asymptomatic, do not have known coronary artery disease and are aged 45-75 years. It may also be considered for borderline risk individuals (10-year cardiovascular risk 5-10%) (Grundy et al., 2018). This should be particularly considered in those where traditionally risk scores may underestimate risk, e.g., in context of family history of premature CVD and possibly in patients with diabetes aged 40 to 60 years old (National Vascular Disease Prevention Alliance, 2012).

In a study to evaluate the usefulness of CACS in CVD risk assessment of airline pilots, Wirawan et al. (2014) compared the results of CACS with the results of the New Zealand Cardiovascular Risk Charts (NZ-CRC) scores in an asymptomatic (non-pilot) population. They found that CACS has a better accuracy (a gain of 0.22 AUC) than the NZ-CRC and reclassified a considerable proportion of asymptomatic patients into correct cardiovascular risk categories. Wirawan et al. (2014) recommended that CVD risk assessment in pilots should be focused on the application of CACS in those with 5-year CVD risk of 5-10% and 10-15% according to the NZ-CRC risk scores.

The 2010 American guidelines on cardiac risk assessment (Greenland et al., 2010) have recommended CAC in asymptomatic patients considered to be at intermediate risk of 10-20% and also suggested that CAC may be reasonable for those who have a 6-10% 10-year risk but not in individuals with <6% risk.

4.2 Computed Tomography Coronary Angiography (CTCA)

Computed tomography coronary angiography (CTCA) has emerged as the non-invasive test of choice for imaging the coronary vasculature, demonstrating clinical efficacy in multiple large-scale randomized clinical trials (Dweck et al., 2016). It provides additional information to CACS regarding stenosis severity and has an incremental prognostic value to CACS in respect of coronary artery events (Arbab-Zadeh & Fuster, 2016; Gaemperli et al., 2008; Van Werkhoven et al., 2009; Taylor et al., 2010).

To use CTCA is more complex than a simple Coronary Calcium Scan; it requires an intravenous contrast injection, and often I.V. β-blocker administration to slow the heart rate to around 60 bpm to optimize image acquisition. With modern scanners, the dose from a CTCA is between 0.2 mSv and 5 mSv depending on the technique and exposure time (Fuchs et al., 2014; Stehli et al., 2014). Radiologists who do not want to use an I.V. β-blocker, need to scan more phases of the heart cycle with consequent longer radiation exposure time and dose. Using the correct techniques and new iterative reconstruction algorithms, it is however possible to keep the radiation dose considerably lower than 1 mSv (Fuchs et al., 2014; Stehli et al., 2014).

CTCA is able to both image and characterize plaques (calcified, non-calcified or mixed). This is a huge advantage of this method because it enables the detection of non-calcified soft plaques, which may cause a sudden cardiac emergency or sudden death due to a plaque rupture without any alarming symptoms before the event (Libby, 2013; Crea & Libby, 2017). Exclusively non-calcified plaques are considered to be present in 4% of asymptomatic individuals (Choi et al., 2008). In symptomatic patients, non-calcified coronary artery plaque was found to be present in up to 10% of the patients with a CAC score of 0 who were also examined using CTCA (Koulaouzidis et al., 2013). Because the presence of non-calcified coronary artery plaque is associated with classic risk factors (Kolodgie et al., 2004; high LDL-cholesterol, positive family history), the initial risk score will indicate further cardiological evaluation in most cases. If in asymptomatic pilots the initial risk score is intermediate or high and the CACS is 0 or low, it is recommended to use CTCA in order to exclude the presence of non-calcified plaques (Parsons et al., 2017; Braber et al., 2016; Gray et al., 2019). Recent advances in CTCA and cardiac MRI (CMR) show promise in the identification of high-risk plaques (Narula et al., 2013; Braunwald, 2015).

Many studies have reported on the sensitivity and specificity of CTCA in detecting obstructive CAD. Although CTCA has a very good efficacy to exclude the presence of coronary artery disease (e.g., Dweck et al., 2016), most studies showed that the specificity decreases significantly with increased calcification. In one study, the specificity dropped to 20% when the CAC score was more than 400 (Phillips & Mieres, 2010). Heavy calcifications may result in blooming artefacts and obscure the view for the reader, resulting in overestimation of lesion severity (encroachment of the lumen) and false positive results (Kuettner et al., 2005). Therefore, if the CACS is greater than 400, consideration should be given to add a test to evaluate the presence or non-presence of coronary ischemia, for example by myocardial Single Photon Emission Computed Tomography (SPECT) after exercise, or by direct invasive angiography, as CTCA may be non-diagnostic for the severity of coronary lesions. And if CACS is greater than 1,000, CTCA is not recommended (Gray et al., 2019).

On a CTCA the presence of obstructive lesions >50% is considered a reasonable aeromedical threshold for - at least a temporary - grounding and further cardiological investigation (Gray et al., 2019). Novel techniques also allow derivation of accurate CACS from CTCA studies, thus providing more information while minimizing radiation exposure (Pavitt et al., 2016). It is important to consider the aggregate stenosis to determine the overall CVD risk. Aggregate stenosis is the sum of quantified stenosis. In the past this was assessed using invasive coronary angiography (ICA), but now it is also possible to determine the aggregate stenoses by CTCA (Nakazato et al., 2013). Generally, the severity of a coronary stenosis does not yet implicate a therapeutic procedure. In the presence of advanced coronary stenosis there is a need to prove that these lesions are related with coronary ischemia; this can be achieved either by non-invasive methods or by coronary-angiography using FFR (Fractional Flow Reserve).

Comparing the cost-effectiveness of frequently used cardiological diagnostic tools, Moss et al. (2017) found that CTCA was by far the lowest-cost test per correct diagnosis due to the low cost of the test and high sensitivity and low probability of fatal or non-fatal complication. The low cost and high sensitivity of cardiac CT make it the test of choice in the evaluation of stable angina. This has now been ratified in national guidelines with NICE recommending cardiac CT as the first-line investigation for all patients presenting chest pain due to suspected coronary artery disease (NICE, 2016).

4.3 Vascular ultrasound imaging: Carotid Intima-Media Thickness (IMT)

Ultrasound imaging of the carotid and femoral arteries provides easily accessible visualization of vascular anatomy without radiation. Intima-media thickness (IMT) of exposed large vessels, such as the carotid arteries, predicts future CVD better than risk factors alone (Chambless et al., 1997). Several prospective studies have shown that the presence of carotid and femoral bifurcation plaques is associated with future cardiovascular events, independent of other risk factors, but studies in which this method has been used have also shown that it has a much weaker predictive power for cardiovascular events compared with CACS (Folsom et al., 2008; Baber et al., 2015), whereas carotid IMT was a stronger predictor of stroke in the Cardiovascular Health Study (Greenland et al., 2010). Wide variability in ability of IMT to predict future CVD events and stroke was found amongst studies, leading to uncertainty regarding its utility (Lorenz et al., 2010; Geisel et al., 2017). This is reflected in consensus statements and guidelines. The 2010 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Greenland et al., 2010) gave carotid IMT assessment a Class IIa (benefit greater than risk) indication in subjects with intermediate-risk (Framingham Risk Scores), whereas the 2013 guidelines gave it a Class III (should not be done) indication (Stone et al., 2014).

Of interest is a newer ultrasound technique: a 3-dimensional (3D) assessment of bilateral carotid arteries seems to have a much better prognostic relevance compared to the classical determination of the IMT of the carotid arteries (Baber et al., 2015; Naqvi, 2015). Recent data show that direct 3D assessment and quantification of carotid plaque is feasible and can be used clinically (Al Muhanna et al., 2014). Baber et al. (2015) showed that ultrasound examination of 3D plaque area was comparable to CACS in predicting CVD death and myocardial infarction.
Because in ultrasound imaging no radiation is involved, it may be more suitable for longitudinal life-long surveillance if no plaque burden is identified in either vascular bed at baseline and may be a first-line test in younger individuals (Naqvi, 2015).

4.4 Second-line investigations for Coronary Artery Disease and CVD

When enhanced screening investigations show evidence of significant CVD, further cardiological investigations have to be done to enable an advice concerning therapeutic measures (Neumann et al., 2018) and the flying status. These investigations must define the severity of the coronary stenosis in cases where CTCA has not yet been used or has not yet given sufficient information, and they must answer the question if coronary ischemia is present or not, and if yes, they must assess the extent of the ischemia.

Investigations for the refinement of the **anatomic** coronary situation generally involve:
- CTCA (see § 4.2);
- Invasive coronary angiography (ICA).

Investigations for the assessment of the presence of **functional** coronary ischemia generally involve:
- Myocardial perfusion scintigraphy (MPS);
- Single Positron Emission Tomography (SPECT) and Positron emission tomography (PET);
- Cardiac magnetic resonance (CMR) (also known as cardiac MRI);
- Invasive coronary angiography (ICA) with application of Fractional flow reserve (FFR) or of the Instant wave-free ratio (iFR);
- Stress echocardiography;

- PET might become the first line method for the assessment of the presence of coronary ischemia in the near future (Jaarsma et al., 2012).

Indications and interpretation concerning above second-line investigations are in the realm of the expert cardiologist who has to choose the optimal diagnostic procedures on a case by case basis. Therefore, further discussion of the second-line investigations is beyond the scope of the present project.

4.5 Conclusion Enhanced Screening

The use of CACS or CTCA allows to detect subclinical coronary atherosclerosis and thus, to identify asymptomatic individuals at increased risk for adverse coronary events. Both methods enhance the risk prediction compared with conventional risk factors (Baber et al., 2015; Arbab-Zadeh & Fuster, 2016; Gaemperli et al., 2008; Van Werkhoven et al., 2009; Taylor et al., 2010; Yeboah et al., 2016; Abdulla et al., 2011; Maire, 2017; Gray et al., 2019).

CACS is a robust and reproducible way of detecting coronary atherosclerosis and to estimate future risk of cardiac events. It has incremental benefit beyond traditional risk prediction tools and biomarkers and can be easily performed. Its greatest benefit is that CACS is able to specify and re-classify risk when applied to asymptomatic individuals between 45-75 years who are at borderline (5-10% 10-year risk) or intermediate risk (10-20%) as determined by an appropriate risk calculator.

- A CACS >100 should result in aircrew being temporarily grounded pending further investigation of the individual cardiovascular risk using methods such as computed tomography coronary angiography (CTCA), myocardial perfusion scintigraphy (MPS), cardiovascular magnetic resonance imaging (CMR), and Invasive coronary angiography (ICA).

CACS has the advantage over CTCA in that it is less expensive, is reproducible, and does not require intravenous contrast. However, CACS data provide no detail on extent and location of coronary stenosis on an individual basis and do not identify non-calcified coronary artery plaques.

CTCA provides information about the number, extent and location of luminal stenosis and, therefore, allows determination of individual risk. However, in cases of extensive calcification (e.g., CACS >400) specificity of CTCA drops considerably because heavy calcifications may result in blooming artefacts and obscure the view for the reader. CTCA facilities may be less accessible in some EU Member States. When available, and in the absence of contra-indications for I.V. contrast or β-blocker administration, it can be considered to use CTCA instead of CACS as a first step of enhanced cardiological screening. This choice would be favoured when the CTCA method also allows for derivation of accurate calcium scores.

Vascular ultrasound imaging and Carotid Intima-Media Thickness (IMT) can provide additive independent risk information in individuals at increased risk, but it should be considered that the predictive power of carotid IMT for cardiovascular events is weak and - in agreement with the ACC/AHA as well as ESC guidelines - it is recommended not to use these techniques to get additional information when screening asymptomatic aircrew.

5 Conclusion/Recommendation

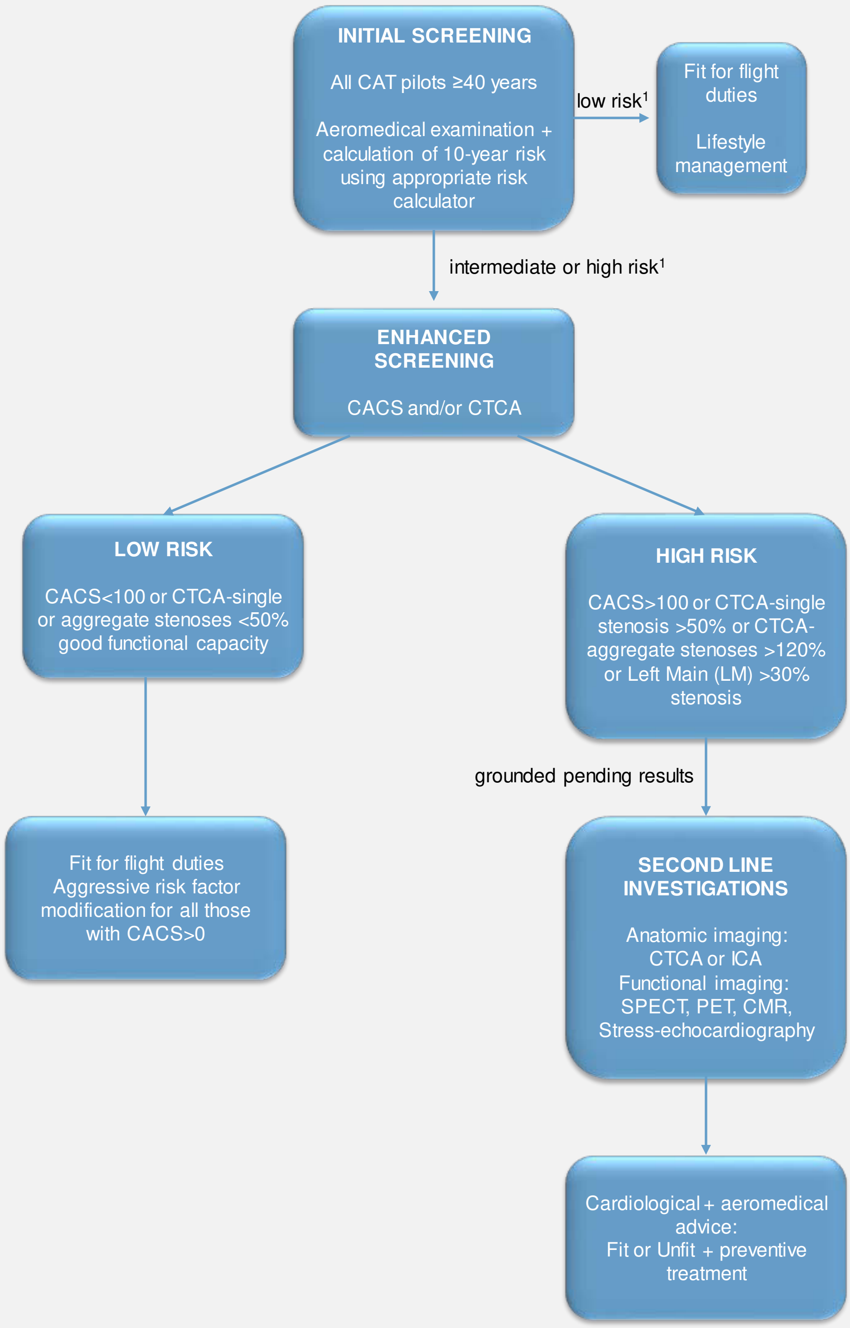
In conformity with clinical standards for appropriately allocating preventive treatment and the recommendations of Maire (2017) and Gray et al. (2019) for CVD risk assessment in aircrew, it is concluded that a stratified cardiovascular risk assessment should be used in order to reduce the in-flight medical incapacitation risk in older CAT pilots.

It is recommended to periodically screen all aircrew, in particular those over the age of 40 years, on cardiovascular risk using a resting ECG and risk estimators (‘calculators’) that are representative and appropriate for the population to screen and include family history and provide non-fatal and fatal endpoints.

In the initial stage of CVD risk stratification an appropriate risk estimation tool can be used to complement the regular aeromedical examination as required by EASA. If the initial risk estimation indicates an intermediate or higher risk level (≥10% 10-year risk of ‘hard’ CVD events), a further cardiological risk assessment will be needed using enhanced diagnostic methods, such as CACS and/or CTCA (see flow chart Figure 1). For pilots of whom the initial risk is estimated to be between 5% and 10% (borderline; Grundy et al., 2018), thorough lifestyle counselling is recommended with emphasis on preventive diet and exercise measures. Aircrew with a CACS >100 or CTCA-single stenosis >50%, CTCA-aggregate stenoses >120%, or Left Main (LM) >30% stenosis should be grounded pending further investigation of the individual cardiovascular risk (see Figure 1). It is recommended that individuals with an initial risk score of >10% and a very low or zero CACS should undergo a CTCA examination in order to exclude the presence of coronary artery disease and risky non-calcified plaques. Use of IMT for additional cardiovascular evaluation is not recommended.

Pilots in a low cardiovascular risk category (<10 %), and/or with a CAC score <100, are considered fit to fly, while it should be considered to give them lifestyle management advice in order to keep their CVD risk low (Figure 1). Stratified risk assessment should be periodically repeated (periodicity dependent of the age).

The exact content of the aeromedical examinations, periodicity, and possible limiting conditions of the license of older pilots will be discussed in the report of Task 4.



[1] The classification of a low, intermediate or high risk is given by the cardiovascular score being used. We recommend using the PROCAM score; in this case a 10-year cardiovascular risk of <10% is low, of 10-20% intermediate and of >20% high.

Figure 1 Flow chart with algorithm adapted from Gray et al. (2019). This algorithm is aimed at supporting AMEs and Medical Assessors. The second line investigations are in the realm of the consulted cardiologist

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Part 4 Conclusions and Recommendations (Deliverable No. 4)

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Content Part 4

1 Introduction

In Task 1 (Simons et al., 2018), it was concluded that the most frequent age-dependent causes of sudden incapacitation include sudden death, coronary artery disease, cardiac arrhythmias, pulmonary embolism, stroke (cerebral ischemic infarction, cerebrovascular accident, and cerebral haemorrhage), syncope, late-onset seizure(s), and acute psychosis.
In Task 2 (Roelen et al., 2018), it was found that the risk of the 55-64 age group is just within the margin of the acceptability limit for catastrophic system failures for single piloted CS23 aircraft with a single reciprocating engine and a seating capacity for 0-6 passengers. As a result, we think there is a need to reduce the medical incapacitation risk of single flying CAT pilots in the 55-64 age range. In addition, we think that any increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet the current operational accident acceptability values. Furthermore, it was concluded in Task 2 that allowing pilots older than 65 years in multi pilot CAT operations would require additional risk-mitigation measures such as specific tests to support the aeromedical decision on the applicant's fitness on an individual basis.
In Task 3 (Simons et al., 2019), it was recommended to periodically screen all aircrew over the age of 40 years on cardiovascular risk using a resting ECG and a risk estimator ('calculator') that is representative and appropriate for the population to screen. In addition, the calculator used should include family history and provide non-fatal and fatal end points. If the initial risk estimation indicates an intermediate or higher risk level (≥10% of 10-year risk of 'hard' CVD events), a further cardiological risk assessment will be needed using enhanced diagnostic methods, such as Coronary Calcium Scanning (CACS) and/or CTCA (see flow chart Figure 1 in the report of Task 3). Aircrew with a CACS >100, CTCA-single stenosis >50%, CTCA- aggregate stenoses >120%, or Left Main (LM) >30% stenosis should be grounded pending further investigation of the individual cardiovascular risk. For pilots of whom the initial risk is estimated to be between 5% and 10% (borderline), pro-active lifestyle counselling is recommended, with an emphasis on preventive diet and exercise measures.

Aim of present report

Based on the conclusions and recommendations composed in Task 1, 2, and 3, the aim of Task 4 is to make concluding recommendations regarding the acceptable age limits for 1) CAT pilots flying single-piloted aircraft; and 2) CAT pilots flying multi-pilot operations, in order to keep the total in-flight incapacitation risk at an acceptable safety level. In parallel to those recommendations, a set of methods will be proposed to enhance identification of pilots at risk, to reduce the risk of total incapacitation, and to decide on the applicant's fitness on an individual basis. In addition, the present report will discuss the implementation of the proposed changes in aeromedical assessments. Moreover, knowledge gaps will be identified and priorities for future research and data gathering will be addressed.

2 Age-dependent Medical Risks Associated with Total Incapacitation

As cardiovascular conditions are considered as the principal risk factor for total incapacitation, the report of Task 3 focused primarily on cardiovascular risk assessment and risk reduction. In the conclusions of Task 1, syncope, late-onset seizure(s), and acute psychosis were also mentioned as possible age-dependent causes of sudden incapacitation. The risk of incapacitation due to these conditions should therefore also be reduced as much as possible. The risk assessment of syncope, late-onset seizure(s), and acute psychosis will be briefly discussed in Sections 2.1-2.3. Section 2.4 addresses the reduction of incapacitation risk associated with age-dependent changes in the sensory system. The consequences and considerations regarding neurophysiological assessments and cognitive functioning are elaborated in Section 2.5. Finally, the effects of long and irregular working hours, and overtime work on both cardiovascular risks and fatigue will be discussed in Section 2.6 and 2.7 respectively.

2.1 Syncope

There is a significant increase in the incidence of syncope after 70 years of age (da Silva, 2014). Among the causes of syncope, the neuro-cardiogenic or vasovagal syncope is the most frequent. The other causes are of cardiac origin, orthostatic hypotension, inadequate circulatory reflex mechanisms, neurological, and psychiatric disorders. Many cases of syncope cannot be prevented by early detection because the cause is not known or it occurs as a reaction to certain circumstances (da Silva, 2014). Detection during the medical screening will have to concentrate on cardiovascular, metabolic and neurological causes, and inadequate circulatory reflex mechanisms (assessment of medical history, measurement of systolic blood pressure and heart rate after rapid change from supine to vertical body position). Possible causes of syncope with a cardiological origin may be identified during cardiovascular risk assessment as discussed in this report.

2.2 Late-onset seizures

In the context of age-dependent risk assessment, the risk of late-onset seizures is assumed to be strongly associated with cardiovascular disease. In older adults, acute stroke is the most common cause of seizures, accounting for up to 50% of the cases (Stephen & Brodie, 2000; Brodie et al., 2009). There is increasing evidence that otherwise unexplained late-onset seizures and epilepsy might represent the first clinical manifestation of an underlying occult cerebrovascular disease. Epileptic seizures can be regarded as a marker of subclinical cerebrovascular disease that has not yet resulted in transient ischemic attack (TIA) or stroke (Brigo et al., 2014). Because of the strong association with cardiovascular diseases, prevention of late-onset seizures will significantly benefit from a systematic cardiovascular risk assessment.

Other causes of seizures, such as brain tumours and metastatic growths, are often difficult to identify in early stages. A thorough neurological history and examination, which should be part of each regular AME screening, might reveal the first subtle symptoms however. In that case neurological consultation should be sought afterwards. The usefulness of brain MRI as part of screening tests for asymptomatic senior pilots has been evaluated by Kagami et al. (2009) who reported on 449 asymptomatic Japanese airline pilots who underwent brain MRI screening mandated by the Ministry of Transport during 2005-2007. Only 3% of the pilots were found to have asymptomatic cerebral infarction on MRI. The authors concluded that the usefulness of brain MRI as part of screening tests for asymptomatic senior pilots was

not clear because of the low prevalence of asymptomatic cerebral infarction in senior pilots compared to the general population and its unclear medical significance.
In the meantime, screening companies have begun to advertise and offer brain MRI scans to the general public. In a review, Komotar et al. (2008) concluded that brain MRI scans should not be recommended for screening healthy populations because of screening bias, low prevalence, poor predictive value, and the limited need and effectiveness of intervention.

2.3 Psychosis

There is no significant evidence for increasing risk of depressive disorder or suicide risk with increasing age (WHO, 2017; ISD Scotland, 2012; Scowcroft, 2017). There appears to be an increase in non-affective psychoses and degenerative brain processes in people over 60 years (Van Os et al., 1995; Brugha et al., 2005). These psychoses generally have a benign course, greater prevalence in women than men, and high prevalence of premorbid psychological and physiological stressors. Non-affective psychoses of the elderly are rare and are characterized by symptoms such as delusions and hallucinations. There is evidence for a connection between degenerative brain processes (e.g., Alzheimer and other forms of dementia) and onset of non-affective psychosis in the elderly (van Os et al., 1995). Risk assessment of these non-affective psychoses and degenerative brain processes should therefore focus on extensive history and psychiatric consultation to reveal any suspicion of psychiatric symptomatology.

2.4 Sensory systems

2.4.1 Vision

The functioning of the visual system changes with age. According to Verriest and Vos (1989), the main changes in the visual system with increasing age are:

- Loss of elasticity and powers of accommodation of the lens;
- Reduction in the light admitted by the pupil;
- Increase in the light diffusion and absorption in the aqueous humour of the eye;
- Biochemical and anatomic change in the retina.

Apart from presbyopia, these changes cause a linear decline in contrast sensitivity with age for medium and high spatial frequencies (Ross et al., 1985) and impaired visual performance as light levels decrease (Gillespie-Gallery et al., 2013). If the amount of light admitted is reduced and the diffusion of light increases, acuity is lost and vision dims. Therefore, with increasing age, more light will be needed to ensure that the same amount of light falls on the retina (Tidbury et al., 2016). From the age of 20 onwards, the eye's ability to adapt to darkness with a long exposure time (>30 minutes) declines by a factor of 5 every 10 years (McFarland & Fisher,1955).
Like contrast sensitivity, acuity and stereopsis, colour vision also changes with age. Age-dependent reduction in the number of cones at the fovea causes generalized reduction in colour vision (Wuerger, 2013). She found that colour-vision abnormalities were uncommon in people younger than 70, but abnormalities were present in about 45 percent of people in their mid-70s, up to 50 percent of those 85 and older, and nearly two-thirds of those in their mid-90s. Nearly 80 percent of the abnormalities involved "blue-yellow" errors. These errors are distinct from the "red-green" errors observed in people with inherited colour blindness. Based on the above-mentioned age-dependent effects on the visual system it is recommended to examine CAT pilots ≥60 years employing contrast sensitivity testing, and dynamic visual acuity tests using different levels of luminance.

2.4.2 Hearing

As people get older, the hearing organ alters; changes first occur in the inner ear and spread to the auditory nerve and the central hearing centres later (Yamasoba et al., 2013). As a result of these changes, there is a gradual decline in the ability to hear high tones (12 kHz) at first, and lower tones (1, 2 and 4 kHz) afterwards. From puberty onwards, the hearing threshold for the speech frequencies shifts by 2-3 dB every 10 years, but in the case of the higher frequency ranges this shift is much greater. A reduction in hearing is generally experienced as a nuisance if it exceeds 25 dB. In cases where there is a reduction of around 40 dB for frequencies of 500-4,000 Hz (speech), the ability to follow a conversation at a distance of 50 cm will be greatly impaired. Prevalence of hearing loss by age in the United States (measured between 2001-2008) is 3% of those aged 40-49; 9% of the 50-59 cohort; 22% of those 60-69 years old; and 50% of the age group 70-79 years (Yamasoba et al., 2013). In this study hearing loss was defined by a pure tone average (PTA) of 500-4,000 Hz thresholds in the better-hearing ear >25 dB.

2.4.3 Consequences of decline of sensory functions for pilots

Pilots who do not satisfy the required criteria for vision and/or hearing fail the medical screening. However, older pilots are seldom excluded due to this criterion; the majority of failures on this account take place either on the first screening or at ages <40 years (Holewijn & Krol, 1992). In older pilots, the decline in the vision and hearing is limited to a level at which they just reach the criteria. These borderline cases manage to score a pass mark when vision and hearing are tested separately, since they are able to concentrate fully on their performance of one task. However, when they are required to concentrate to an exceptional extent on one of these faculties in a situation in which they have to perform complex tasks (for example during flight), they may not pay sufficient attention to their other tasks. This channelling of attention could result in subtle incapacitation (Simons et al., 1996). At present, the capacity of the vision and hearing system of pilots is tested separately during medical screening. As a result, it is possible to determine whether each individual fulfils the absolute criteria imposed in this respect. However, these tests provide no information about the dynamic functioning of both systems. In borderline cases this screening should therefore be expanded and include tests that cover the dynamic functions of vision and hearing in the performance of a range of flight tasks. Due to the multiple task principle, the hearing and/or vision of the pilot is tested while he/she has to perform flight-related tasks simultaneously. This will enable to determine whether pilots who barely fulfil the vision and hearing criteria run a greater risk of subtle incapacitation (Simons et al., 1996).

2.5 Neuropsychological assessment and cognitive functioning

Neuropsychological assessment is a performance-based method to assess cognitive functioning. This method is used to examine the cognitive consequences of brain damage, brain disease, and mental illness. There are several specific uses of neuropsychological assessment, including collection of diagnostic information, differential diagnostic information, assessment of treatment response, and prediction of functional potential and functional recovery. Neuropsychological testing is also an important tool for examining the effects of toxic substances and medical conditions on brain functioning.
Neuropsychological tests have generally accepted diagnostic value in patients with symptoms or a suspected history (both to be identified by the AME), but these tests have never been developed as a ‘pass’ or ‘fail’ instrument in the context of screening individuals for highly skilled jobs. Therefore, a meaningful interpretation of results in asymptomatic individuals is impossible as there are no validated cut-off points beyond which a safe (flying) performance can be predicted.

The relationship between basic domain-independent cognitive abilities and flight performance is very complex. Functions assessed in cognitive aging studies represent basic, domain-independent, cognitive

abilities that are only one factor in determining flight performance. Higher order cognitive factors, including metacognitive skills and domain-specific knowledge, may play an equal or greater role in determining flight performance (Hardy & Parasuraman, 1997). Static measures of cognitive functioning typically obtained in laboratory tests may not be representative of the more complex and dynamic cognitive processes required in real-world tasks.
Age-related differences in measures of pilot cognition are minimally predictive of primary measures of flight performance and there is generally a low predictive validity of laboratory cognitive measures to flight performance (e.g., Damos, 1996). Cognitive ability (including perceptual-motor skills) is moderately associated with job proficiency (see Hunter & Hunter (1984) for review).

Pilot flight performance is the product of domain-independent skills (basic cognitive abilities) and, to a greater extent, domain-dependent knowledge and it is concluded that the weak correlations between these two are not caused by the fact that cognition is unrelated to flight performance, but because the standard cognitive tests are insufficient to capture the complexity and dynamism of the cognitive skills involved in flying an aircraft (Hardy & Parasuraman, 1997).

When examining age and expertise level effects in flight simulator performance, it is expected that expertise will be more likely to aid older expert pilots' performance on perceptual-motor tasks and tasks that are relatively unconstrained by time (Kennedy, 2010). In a flight simulator study, Taylor et al. (2007) found that more expert pilots had better flight summary scores at baseline and showed less decline over time. Regarding age, even though older pilots initially performed worse than younger pilots, over time older pilots showed less decline in flight summary scores than younger pilots. Secondary analyses revealed that the oldest pilots did well over time because their traffic avoidance performance improved more as compared to the younger pilots. Taylor et al. (2007) concluded that their findings support previous cross-sectional studies in aviation as well as non-aviation domains, which demonstrated the advantageous effect of prior experience and specialized expertise on older adults' skilled cognitive performances.

When the cognitive functioning of an individual is evaluated, it is important to have information about the occupational history of that person. Data that are relevant in this context are the functioning of the pilot in the event of incidents and accidents and during simulator sessions, proficiency checks and training courses. These data may be provided by the airline or authority to the screening physician with the permission of the pilot concerned. Such data are an important aid in detecting deterioration in cognitive functioning in the course of time. If the data over a relatively long period are systematically examined, it is possible to identify when structural deterioration of performance occurs. When the performance of a previously perfect performing pilot starts to impair during simulator sessions and he/she scrapes through proficiency checks and/or is more frequently involved in incidents, the screening physician is alerted to a structural deterioration of functioning (for example caused by incipient dementia). After discussion with the pilot concerned, the physician can refer him/her for neurological or neuropsychological examination. This procedure enables identification of an impairment of relevant cognitive functioning, irrespective of the cause.

2.6 Long working hours, irregular working hours, and overtime work

There is evidence that frequent exposure to long working hours (≥55 hours per week) or frequent overtime work (3-4 hours overtime) is associated with increased risks of fatal and non-fatal coronary heart disease (CHD), stroke, and atrial fibrillation (Virtanen et al., 2010; Kivimäki et al., 2015; Kivimäki et al., 2017). The meta-analysis of Kivimäki et al. (2015) on CHD comprised data of 603,838 men and women who were free from CHD at baseline and were followed for an average of 8.5 years. They also followed 528,908 men and women who were free from stroke at baseline for 7.2 years. The data were adjusted for age, sex, and socioeconomic status, and working standard hours (35-40 hours per week) were compared with working long hours (≥55 hours per week). Working ≥55 hours per week was associated with an increase in risk of incident CHD (relative risk [RR] 1·13, 95% CI 1·02-1·26) and incident stroke (RR 1·33, 95% CI 1·11-1·61). Kivimäki et al. (2015) recorded a dose-response association for stroke, with RR estimates of 1·10 for 41-48 working hours, 1·27 for 49-54 working hours, and 1·33 for 55 working hours or more per week compared with standard working hours. In addition to these findings, the IPD-Work Consortium found that individuals who worked ≥55 hours were more likely to develop atrial fibrillation than those working standard hours (Hazard Ratio = 1.42, 95% CI = 1.13-1.80) (Kivimäki et al., 2017). Virtanen et al. (2010) found that 3-4 hours overtime work per day was associated with 1.67-fold (95% CI 1.02-2.76) increased risk of fatal cardiovascular disease and incident non-fatal myocardial infarction in a large population of civil servants, with an average follow-up of 11 years.

In a systematic review and meta-analysis of 34 studies with 2,011,935 people, Vyas et al. (2012) found that being exposed to irregular working hours (shift work) was associated with myocardial infarction (risk ratio 1.23, 95% CI 1.15-1.31) and ischaemic stroke (RR 1.05, 95% CI 1.01-1.09). Coronary events were also increased (RR 1.24, 95% CI 1.10-1.39).

Virtanen et al. (2018) found that long working hours (>10 hours on ≥50 days/year) were associated with higher anthropometric markers (BMI, waist circumference and waist/hip ratio), adverse lipid levels, higher glucose, creatinine, white blood cells and higher alanine transaminase in >75,000 male and female employees in France. A dose-response pattern with increasing years of working long hours was found for anthropometric markers, total cholesterol, glucose and γ-GT. It was concluded that men who work long hours might become a risk group with an adverse cardiometabolic risk profile.

Because the effects of long working hours and overtime work of pilots result in an increase of cardiovascular risk factors, the incapacitation risk concerning long working hours will be heralded by a higher CVD risk score using a risk calculator. The same reasoning applies to the increased cardiovascular risk of irregular working hours. Especially since multiple studies, such as those of Esquirol et al. (2011) and Asane-Anane et al. (2015), have reported significant increase of traditional risk factors in shift workers, such as higher blood pressure, higher LDL-cholesterol and triglyceride levels, and body mass index.

In the context of the association of long work hours, overtime work, and shift work with an increased CVD risk, some authors recommend countermeasures such as a limit of operation time to 40 hours/week and duty time to 10 hours within 24 hours (Virtanen et al., 2018). Although we agree that such operational limitations could be considered to apply for pilots from the age of 60 onwards, it will not reduce the accumulative CVD risk after numerous years of exposure to long and irregular working hours. A working hour limitation could, however, lead to a reduction in fatigue and an increase in the recovery of older pilots.

2.7 Fatigue

Fatigue occupies a special place in the range of mental problems that adversely affect cognitive functioning (e.g., undue stress and relational difficulties). Acute severe fatigue or chronic fatigue can result in subtle incapacitation: the fatigued individual tries to fight off sleep and cannot concentrate on what he/she is doing. The fatigue which afflicts pilots is caused by the cumulative effects of lack of sleep and irregular and long working hours. The adverse effects of lack of sleep on the performance of tasks have been adequately described in the past (Perelli, 1980; Rosekind et al., 1992). Serious disorders of this kind should be detected during a medical screening of pilots. There are major differences between individuals in terms of tolerance to disruption of the circadian rhythm and lack of sleep. It is, however, known that with increasing age, employees tend to need more time to recover from these aspects of working with long and irregular working hours (Saksvik et al., 2011). Van Drongelen et al. (2016) showed that this holds for older commercial pilots as well, as the risk for chronic fatigue increased with age.

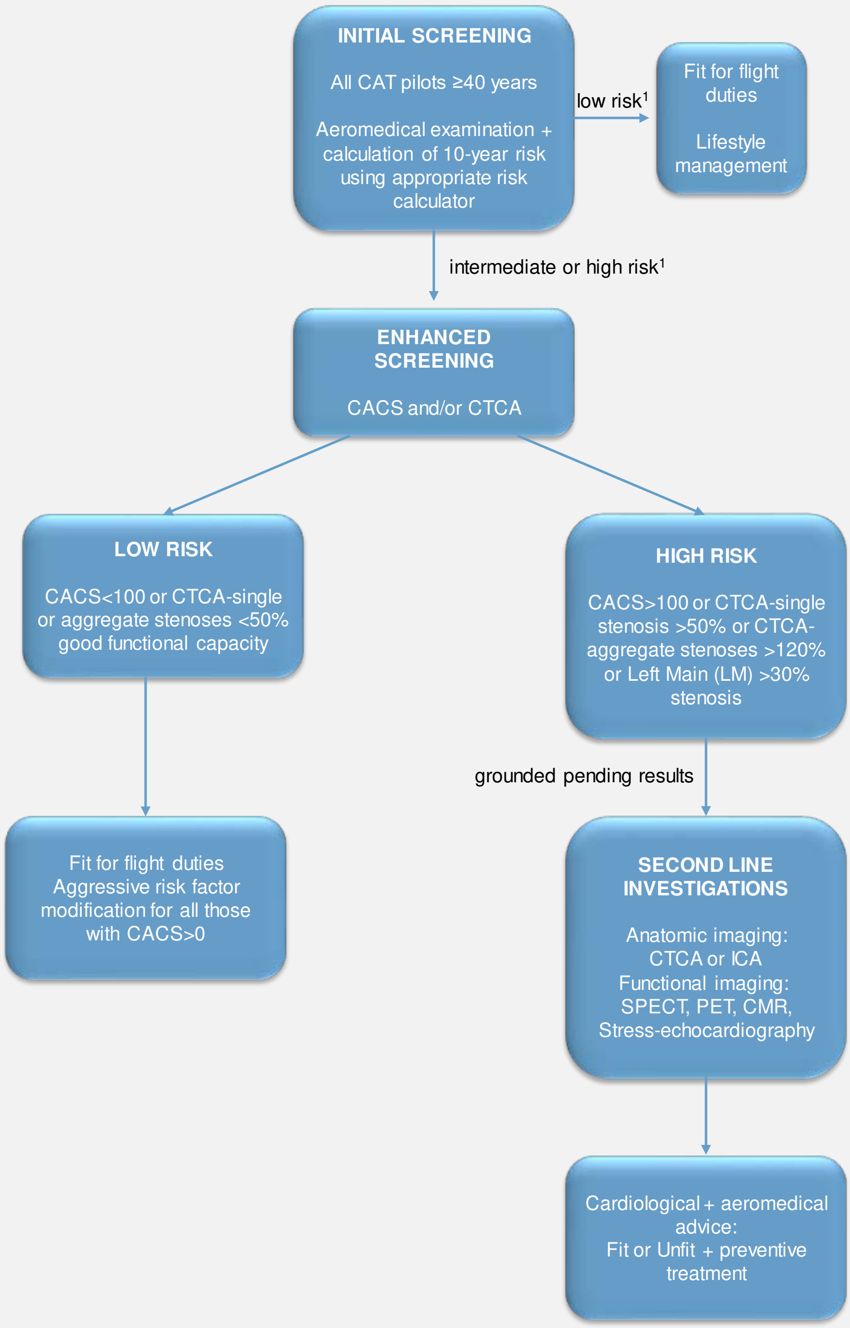
3 Conclusions and Recommendations for Preventive Measures and Age Limitations

The current EASA FCL.065 Curtailment of privileges of license holders aged 60 years or more in commercial air transport states the following (EASA, 2016):

a. Age 60-64. Aeroplanes and helicopters. The holder of a pilot licence who has attained the age of 60 years shall not act as a pilot of an aircraft engaged in commercial air transport except as a member of a multi-pilot crew;
b. Age 65. Except in the case of a holder of a balloon or sailplane pilot licence, the holder of a pilot licence who has attained the age of 65 years shall not act as a pilot of an aircraft engaged in commercial air transport.

3.1 Recommended preventive measure for all pilots ≥40 years of age

Early prevention of cardiovascular disease is considered to reduce the number of pilots at risk for incapacitation. As mentioned in the report of Task 3 (Simons et al., 2019) and in accordance with ICAO recommendations on prevention (Jordaan, 2017), it is recommended to periodically screen all aircrew over the age of 40 on cardiovascular risk using a resting ECG and risk estimators ('calculators') that are representative and appropriate for the population to screen and include family history and provide non-fatal and fatal end points. When the risk score is ≥10%, enhanced screening methods should be used to further evaluate the individual CVD risk, possible preventive measures, and fitness to fly (see flow chart of Figure 1). For pilots of whom the initial risk is estimated to be between 5% and 10% (borderline risk), pro-active lifestyle counselling is recommended, with an emphasis on preventive diet and exercise measures.



[1] The classification of a low, intermediate or high risk is given by the cardiovascular score being used. We recommend using the PROCAM score; in this case a 10-year cardiovascular risk of <10% is low, of 10-20% intermediate and of >20% high.

Figure 1 Flow chart with algorithm adapted from Gray et al. (2019). This algorithm is aimed at supporting AMEs and Medical Assessors. The second line investigations are in the realm of the consulted cardiologist

3.2 Recommended age limitations

3.2.1 CAT pilots flying single-piloted aircraft

Based on the outcome of Task 1 and 2 it was concluded that the risk of the 55-64 age group is just within the margin of the acceptability limit for catastrophic system failures for single piloted CS 23 aircraft with a single reciprocating engine and a seating capacity for 0-6 passengers; and therefore, there is a compelling need to reduce the medical incapacitation risk of single flying CAT pilots in the 55-64 age range and any increase of the age limitation for single pilot operations should be accompanied by additional measures to reduce the likelihood of pilot incapacitation to meet current operational accident acceptability values.

It is recommended to extend the age limit of CAT pilots flying single pilot operations from 60 years to the pilot's 65th birthday. A medical screening should be done every six months as is currently required for single flying CAT pilots from the age of 40 onwards (MED.A.045).

Table 1 shows the recommended general medical examinations as well as the additional examinations. As an additional operational/functional requirement to the specific medical procedures, the pilot should be required to successfully pass a proficiency check or a simulator check (Licence Proficiency Check - LPC or an Operator Proficiency Check - OPC) every 6 months from age 60 to age 65. This is in agreement with the widely accepted assumption that six-monthly simulator checks are better than a medical or psychological exam at checking cognitive performance and detecting pilots who fall below required standards, particularly if combined with line checks and peer review (Evans, 2011).

Table 1 Recommended general medical examinations for Class 1 CAT pilots aged 60-65 with single and multi-pilot operations

Timing of routine examination	Complete general aeromedical examination	12-lead ECG	Blood lipids & blood sugar	Cardiovascular risk estimation	Specialist ophthalmological examination	Audiometry	Spirometry	LPC or OPC
Age								
60	✓	✓	✓	✓	✓	✓	✓	✓
60.5	✓							✓
61	✓	✓	✓	✓				✓
61.5	✓							✓
62	✓	✓	✓	✓	✓	✓		✓
62.5	✓							✓
63	✓	✓	✓	✓				✓
63.5	✓							✓
64	✓	✓	✓	✓	✓	✓		✓
64.5	✓							✓
65	Class 1 medical certificate expires							

3.2.2 CAT pilots flying multi-pilot operations

Based on the outcome of Task 1 and 2, it was concluded that allowing pilots older than 65 years in multi-pilot CAT operations would require additional risk-mitigation measures such as specific tests to support the aeromedical decision on the applicant's fitness on an individual basis. We recommend keeping the age limit at 65 years as it is currently set by EASA (FCL.065; EASA, 2016).
It is currently not recommended to further relax or completely abolish the 65-year age limit because:

- The recommended method for systematic cardiovascular risk assessment is considered to reliably identify the CVD risk for each pilot up to the age of 65 years. It is, however, considered prudent to start with this new procedure and only consider further extension of the age limit beyond 65 after having collected sufficient data that confirm the efficacy and cost-effectiveness of the stratified cardiovascular risk assessment procedure in pilots up to 65 years of age (see Section 4.1). Age-related cognitive decline is not generally marked before the age of 70 (Nicholson et al. (BMA), 2016) and the increase in individual variation in physical fitness and cognitive functioning is assumed to become more manifest after 65-70th year (Hänninen et al., 2002; EURODEM). Beyond the age of 65 the variability of physical and mental/cognitive health determinants increases. The number of pilots at risk for physical (cardiovascular) and mental ailments will therefore increase and medical examination will only detect a proportion of serious conditions. As a consequence, the likelihood of missing a high risk case is considered to increase above 65 years of age;
- Except for cases with clear pathology, there are currently no relevant and sensitive tests to identify subtle impairments in cognitive functioning that are associated with flight safety. At the moment, it is assumed that simulator checks, line checks, and peer review are good at detecting below standard performance. However, published data for this assumption are lacking (Evans, 2011);
- To enable abolition of the upper age limit, further research should be done first, in order to evaluate the effectiveness of the medical risk assessment procedures as recommended in the present report. Furthermore, sufficiently sensitive dedicated simulator checks and or cognitive tests should first be developed to enable proper evaluation of relevant individual cognitive and mental abilities (see Section 4);
- The age of 65 is a socially accepted retirement age, which provides a pilot an acceptable reason to stop when he/she is still proficient. It would be a personal tragedy for a pilot to be forced to stop because of impaired cognitive performance or failure(s). There is a potential for many careers to end in 'failure' when the upper age limit would be extended or completely abolished (Evans, 2011).

The general medical examinations as well as the additional examinations and periodicity for multi-crew pilots between 60 and 65 years of age can be seen in Table 1 as well. In addition, as an Operational/ Functional requirement, CAT pilots should be required to successfully perform a Licence Proficiency Check (LPC) or an Operator Proficiency Check (OPC) every six months from age 60 to age 65.

3.3 Content of recommended additional examinations

3.3.1 Complete general aeromedical examination

A comprehensive risk assessment should include a full clinical history and physical examination of which the contents are laid down in EASA Part-MED.A.010 (EASA, 2019) and the Acceptable Means of Compliance and Guidance Material. This general aeromedical examination should cover all factors associated with incapacitation risk. Apart from the possible medical complaints, the AME needs to question about a variety of issues in order to identify 'red flags' concerning physical or mental health risks. These issues concern the applicant's job (type of flying, satisfaction, workload, etc.), commuting (home-work), financial worries, sleep, medication, drugs/alcohol/smoking habits, exercise and diet, family arrangements (married? children?), security (fears?), hobbies, and holidays. Information should be gathered to be used for calculation of a risk score and other modifiable and non-modifiable risk factors to be considered in making a clinical judgement about the individual's total CVD risk. Smoking status, blood pressure, serum lipids, waist circumference and BMI, nutrition, physical activity level, and alcohol intake are considered as modifiable risk factors, while age, gender, family history of premature CVD, and social history are considered as non-modifiable risk factors. Related conditions that could contribute to CVD risk, such as diabetes, chronic kidney disease, familial hypercholesterolemia, and the presence of atrial fibrillation (AF) should also be considered.

3.3.2 12-lead resting ECG

A routine 12-lead resting ECG is recommended to identify abnormal conduction or other arrhythmogenic patterns that could increase the risk of cardiovascular incapacitation in aircrew such as left bundle branch block, WPW-syndrome, cardiomyopathies as hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy, or inherited diseases such as long or short QT syndromes and Brugada syndrome. However, a resting ECG is not a good discriminator for the prediction of acute coronary events in asymptomatic adults at low risk of cardiovascular events, and should therefore not be used to predict the 5- or 10-year risk of coronary disease in asymptomatic aircrew.
The use of exercise stress testing in the initial screening of aircrew is not recommended, but may be useful for an enhanced screening procedure.

3.3.3 Blood lipids and blood glucose

To identify cardiovascular risks laboratory investigations should include total cholesterol (fasting), HDL and LDL fractions, triglycerides, and blood glucose (fasting), while it also may be considered to measure high sensitivity C reactive protein (hs-CRP) and/or apolipo-protein B which are significant markers of cardiovascular risk. They can be used to 'enhance' an intermediate risk found with a risk calculator to a higher risk level when C-reactive protein (high-sensitivity assay) is ≥2.0 mg/L or apolipo-protein B is ≥130 mg/dL.

3.3.4 Cardiovascular risk estimation

For screening of European CAT pilots the PROCAM algorithm appears to be an appropriate risk score system for CVD, because the endpoints concern all CVD events (fatal + non-fatal) and the algorithm can be adapted for usage in many European countries, thereby estimating CVD risk of a derivation cohort that is representative for the nationality in question (e.g., online version
http://www.kardiolab.ch/MONICA-PROCAM3_RA1.html).
To calculate the risk score one needs to fill in age, HDL-cholesterol, LDL-cholesterol, triglycerides, systolic blood pressure, smoker yes/no, diabetes mellitus yes/no or fasting blood glucose >6.66 mmol/L, and premature coronary artery disease in 1st degree family (male <55 years; female <65 years). Moreover, one needs to fill in the regional adjustment factor. When the risk score is ≥10%, enhanced screening methods should be used to further evaluate the individual CVD risk (see flow chart in Figure 1).

3.3.5 Specialist ophthalmological examination

In addition to the routine eye examination required in the context of the annual general aeromedical examination, a comprehensive eye examination by an eye specialist is required at reaching 60 years of age and once in every two years thereafter. This additional examination should include:

- History;
- Visual acuities - near, intermediate and distant vision (uncorrected and with best optical correction if needed); to be developed: dynamic visual acuity tests using different levels of luminance and/or distraction by other task;
- Examination of the external eye, anatomy, media (slit lamp) and fundoscopy;

- Ocular motility;
- Binocular vision;
- Contrast sensitivity (*in addition to current requirements*)
- Colour vision with different levels of luminance (addition to current requirements);
- Visual fields;
- Tonometry on clinical indication.

3.3.6 Audiometry

In addition to the routine hearing examination as required in the context of the annual general aeromedical examination, a comprehensive oto-rhino-laryngological examination by a specialist will be required at reaching 60 years of age and once every two years thereafter. This additional examination should include:

- History;
- Clinical examination including otoscopy, rhinoscopy, and examination of the mouth and throat;
- Tympanometry or equivalent;
- Clinical assessment of the vestibular system;
- To be developed: a valid and reliable dynamic hearing test using relevant background noise and ATC communication while performing a distracting task.

3.3.7 Spirometry

At reaching age 60, a spirometry examination is required once to update the lung function. An FEV1/FVC ratio less than 70% at this examination should require evaluation by a specialist in respiratory diseases.

3.3.8 Additional neurological examination by a specialist

A thorough neurological history and examination (including reflexes, sensation, power, vestibular system - balance, Romberg test, etc.) as required in the context of the annual general aeromedical examination is considered to be sufficient in order to assess neurological risk in **asymptomatic** pilots. The major neurological risks for acute incapacitation are acute stroke and late-onset seizures. The stroke and transient ischemic attack (TIA) risks will be adequately assessed using the cardiovascular risk calculation. The risk of late-onset seizures is also considered to be strongly associated with cardiovascular disease (Stephen & Brodie, 2000; Brodie et al., 2009). Epileptic seizures can be regarded as a marker of subclinical cerebrovascular disease that has not yet resulted in TIA or stroke (Brigo et al., 2014). Because of the strong association with cardiovascular diseases, prevention of late-onset seizures will significantly benefit from the systematic cardiovascular risk assessment.
Other causes of seizures, such as brain tumours and metastatic growths, are often difficult to identify in early stages when there are no discernible symptoms to be found in neurological history and examination. Therefore, in case of subtle symptoms, neurological consultation should be sought.
The usefulness of brain MRI as screening test for **asymptomatic** senior pilots is not clear, because of the low prevalence of asymptomatic cerebral infarction in senior pilots compared to the general population and its unclear medical significance (Kagami et al., 2009). In a review, Komotar et al. (2008) concluded that brain MRI scans should not be recommended for screening healthy populations because of screening bias, low prevalence, poor predictive value, and limited need and effectiveness of intervention.
In conclusion, a specialist neurological examination is not recommended in asymptomatic pilots.

4 Considerations and Future Directions

4.1 Availability of Medical Screening Data of National Authorities

In the present project it was found that the majority of the European National Aviation Authorities (NAAs) were unable to provide their medical evaluations data concerning CAT pilots. Reasons given were inaccessibility of the data and inability to retrieve the data. Therefore, it is recommended to improve the system in order to enable a sound evaluation of medical screening results from CAT pilots.

a) National authorities should be enabled to register all data concerning medical evaluations of CAT pilots in an easily accessible format in order to assess trends in age-dependent medical conditions and to evaluate the effects of medical flight crew licensing requirements. An inventory should be made of existing systems and/or methods, with special reference to accessibility and user-friendliness. Proper accessibility of the NAA databases is a pre-requisite for the evaluation of the effectiveness of the cardiovascular and other risk assessment procedures. Such evaluation is essential for future considerations concerning raising or abolishing age limits for CAT pilots (see also Section 3.2.2).

b) Because it is foreseen that developments to improve the accessibility of the NAA databases as mentioned above under a) are likely to take time, it is recommended to start already with a follow-up study aimed at assessing the risk factors and incidence of incapacitating events. For this study, pilots who are currently aged 63-65 years could be monitored during a predefined number of years, also covering the post-retirement period.

c) Because the systematic cardiovascular risk assessment as recommended in the present report should be evaluated on efficacy and cost-effectiveness, national authorities should collect the data of all individual scores of the cardiovascular risk calculation (done in the initial screening) and the consequences of the score as well as the outcome of enhanced screening.

4.2 Follow-up system Pilot's Health

In most Member States it is impossible to do a complete evaluation of the accuracy of the medical decisions taken by the NA, AeMC, AME. This is due to the very limited possibilities for medical follow-up of pilots who have stopped flying due to health problems without informing the NA or AeMC, death and cause of death of retired pilots. It is expected that such follow-up might be hindered by national legislation (privacy, etc.). In a research project an inventory of opportunities, limitations and methods to collect these data should be made.

4.3 Optimize registration of in-flight incapacitation occurrences

In the present project it was concluded that the usefulness of the ECCAIRS database to identify medical and age-dependent causes of in-flight incapacitation was very limited. In many cases information on age, (medical) cause, and operational consequences was lacking. Therefore, general population data were used to make risk estimations. It is recommended to improve the system in order to enable a sound evaluation of medical in-flight incapacitation risks.

4.4 Sensitivity and validity of dedicated simulator checks and neuropsychological assessment

In addition to evaluation of medical risk assessment procedures, research and developments should concern development of sufficiently sensitive and valid dedicated simulator checks and/or cognitive tests in order to consider further extension of the upper age limits for CAT pilots.

Some national authorities who already allow single flying CAT pilots to continue flying until 65 years of age mandate an ‘extended psychological test including cognitive skills’, or ‘psychological testing’, or ‘assessment of cognitive abilities’. Although it is understandable that such tests might ease one’s feeling of safety, this is currently not recommended in the present report. Currently, it is assumed that simulator checks, line checks, and peer review provide the best opportunities to detect below standard performance.

The recommended research should be aimed at incorporating assessment of essential cognitive factors of flight performance in the regular mandatory License Proficiency Checks (LPC) or Operator Proficiency Checks (OPC). Attention should be focused on abilities to function under highly stressful demands, such as high time pressure. In that context, it is recommended to develop a framework for assessing and scoring cognitive performance based on results of the proficiency checks.

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