Supplementary File 1. The rate of normal organ function decline with advancing age: protocol for a systematic review.

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Key Words
Normal ageing, organ function, age-related decline

ABSTRACT

Background The unprecedented rise in life expectancy in the last few decades has led to an increasing proportion of elderly people. Elderly individuals present a particularly complex challenge to health care due to their multiple comorbidities, frailty as well as their functional decline. In order to better understand and guide the care of geriatric patients, it is necessary to understand the natural rate of decline of various organ functions, so as not to inappropriately label them as having disease. This protocol is for a systematic review, which aims to calculate the rate of annual decline of lung, liver and pancreatic function as well as bone mineral density.
Methods An electronic literature search will be conducted in MEDLINE, EMBASE AND CINAHL from inception. Reference lists of included studies will also be searched for relevant prospective cohort studies and randomized controlled trials, which meet the pre-specified inclusion and exclusion criteria. The article selection and risk of bias of included studies will be determined independently by two reviewers. If possible, a meta-analysis will be conducted to pool estimates on the overall rate as well as the decade-specific rates of decline of the specified organ functions in a healthy aging cohort, and compare these estimates with cohorts that are exposed to risk factors.
Discussion This review aims to determine the rate of decline of organ function with age, and determine any predictors of decline. The results from this review will enable clinicians to better differentiate

between physiological age-related decline and pathological decline when interpreting laboratory test results. This will prevent the overdiagnosis of elderly people with diseases that in fact represent normal ageing.

Systematic review registration PROSPERO CRD42018087066

BACKGROUND

Description of the condition

Advances in modern medicine have resulted in unprecedented rise in life expectancy. The average person's life expectancy has risen by 5 years in the last fifteen years alone, the fastest rate of growth since the 1960s[1]. This has led to a rise in the number and proportion of persons aged 65 years and older with multiple chronic conditions and frailty, posing a complex social and economic challenge to healthcare systems.

Ageing is accompanied by physiological changes in the function of most (if not all) organs and senses. The physiological functions of some organs, including the lungs and kidneys, have been documented to reach a peak in early adulthood and then decline thereafter with age[2]. The rates of age-related functional decline are dependent on a number of factors, including genetics and environmental factors[3,4].

Measured lung function parameters decrease with age, due to factors such as loss of elasticity, weakened muscles of respiration and decreased surface area for alveolar gas exchange[6]. Several longitudinal studies have been performed to monitor and calculate the rate of FEV_1 (Forced expiratory volume in 1 second) decline, and highlight those who are at risk of developing disease[3,7,8].

The liver also demonstrates measurable changes with age, with liver weight reported to decrease by as much as 20% after the age of 50 years[2]. Although some studies show that liver function tests do not change with age[2,9,10], it is also established that albumin,- which is a marker of synthetic liver function, decreases with age (though this may in part, be due to other factors such as malnutrition or renal losses[11]). It has also been shown that the liver metabolises drugs slower in aged cohorts compared to younger cohorts[2,12,13].

With advancing age, there is a progressive loss in number and function of insulin-producing beta-cells in the pancreas. This, coupled with increasing systemic insulin resistance in glucose receptors can result in the development of diabetes mellitus in the elderly[14]. Few studies have demonstrated this by monitoring healthy individuals for the development of impaired glucose tolerance or fasting glucose[15].

Bone mineral density measurements also exhibits change with age, resulting in an increased risk of developing osteoporosis, which predisposes older people to minimal trauma fractures. Females have an accelerated decline of bone mass after the onset of menopause, due to declining oestrogen levels. Other factors, such as vitamin D, calcium levels, parathyroid gland function, renal function and gastrointestinal absorption also play a role in maintaining bone mass and skeletal function[16].

Normal ageing may result in changes in laboratory test values and biomarkers, but these changes do not necessarily represent clinical impairment.[5] Even if laboratory tests show values that lie outside the reference ranges, organs have functional reserves that cannot easily be measured by standard laboratory testing. Laboratory test results should not be used as the sole basis for which a diagnosis of disease is made; rather, these values should be integrated with the patient's clinical symptoms in order to make a diagnosis.[5] A measured decrease in organ function also may not represent clinically significant decline, instead demonstrating the normal process of ageing. One explanation for this may be that the demands of the elderly cohorts' activities of daily living are no longer the same as their younger counterparts.

Why it is important to do this review

Elderly people have increasingly been labelled with conditions such as prediabetes, chronic airways disease, osteopenia or liver disease as a result of laboratory testing. Although these conditions may represent a risk of progression to serious disease, which causes premature death, in many cases they may never progress to symptomatic disease and may even represent an expected level of function at that age.

A commonly-reported example is in chronic kidney disease, which is arbitrarily diagnosed by an eGFR (estimated glomerular filtration rate) threshold less than 60ml/min/1.73^2 for more than 3 months. There are no adjustments to this eGFR threshold for age, race or gender. Over 45% of the population over the age of 70 years have a diagnosis of chronic kidney disease according to this threshold[17,18]. Many of these individuals, however, never develop kidney failure or end stage renal disease, and have been inappropriately labeled (overdiagnosed) as having disease[19].

It is important to distinguish pathological aging from physiological decline. Some measures of organ function (such as eGFR) are not calibrated by age or gender, causing overdiagnosis of healthy individuals with disease, which may never manifest or cause harm, and subsequent overtreatment. It is therefore important to clarify what constitutes normal for healthy, aging individuals. To our knowledge, no systematic review has been done to identify and compare the rates of functional decline across organs, and whether there are risk factors/predictors that are in common.

OBJECTIVE

This review aims to determine the average rate of decline of lung function, liver function, pancreatic endocrine function and bone mineral density in healthy individuals with advancing age.

METHODS

Eligibility criteria

Types of studies

This review will consider prospective cohort studies or randomised controlled trials, which employ longitudinal designs (only if they include a control arm that does not receive treatment) with a minimum

duration of three years and three separate measurements. Studies that report the age-related decline of the specified organ functions will be eligible for inclusion, irrespective of publication status and language of publication.

Types of participants

Studies will be considered eligible for inclusion if they follow a cohort of adults to the age of 65 years or more. Participants who have a known risk factor, medical illness or pre-disease specific to the outcome being studied (i.e. participants with diabetes when investigating pancreatic function decline) will be excluded. Appropriate participants will be included irrespective of sex or ethnicity. Studies including pregnant women or children will be excluded.

Type of exposure

We will include studies involving ageing adults with no known comorbidities. Studies will be eligible for inclusion if they follow a normal cohort. Studies that only followed cohorts with risk factors or known exposures and did not compare them to a normal cohort will be excluded. We plan to assess whether there are certain predictors of decline that organs have in common. Examples of risk factors may include:

- Smoking
- Symptomatic hypertension
- High BMI
- Hyperlipidemia
- Diabetes mellitus
- Alcohol consumption

Types of outcome measures

We will include studies which report annual decline, or repeated measurements of organ function over time, to at least the age of 65 years. Studies should record a minimum of three measurements of organ function. Examples of these parameters include:

- Forced expiratory volume in 1 second (FEV_1) for lung function
- Albumin as a marker of synthetic liver function
- Fasting blood sugar levels for pancreatic endocrine function
- Bone mineral density

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Electronic searches

We conducted electronic searches of MEDLINE, EMBASE and CINAHL databases from inception through to October 2017, using the search strategy at the end of this document. This was developed with the assistance of an information specialist.

Searching other resources

Electronic searches were complemented by manual searching through reference lists of studies that were identified for potential inclusion as well as backwards and forward searching.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two authors will independently screen titles and abstracts of all studies identified by the searches for potential inclusion. Prior to commencing screening, a small subset of 50 titles will be screened by the two reviewers as a calibration exercise to check for >80% agreement. After screening, a calibration exercise will be conducted screening the full texts of the studies targeting >80% agreement. The remaining full texts will then be retrieved and reviewed independently by the authors to determine eligibility for inclusion. Disagreements will be resolved by discussion or with another reviewer. If there are multiple reports of the same study, the most recent publication with longest length of follow up will be included.

Data extraction and management

Two authors will independently extract data from the studies using a data extraction form. This form will be piloted using ten studies prior to data extraction as a calibration exercise to check for adequate agreement (>80%) between the reviewers. Data extraction will be performed using Excel and any disagreements will be resolved by discussion or by another reviewer. Extracted measures will include setting and year of the study, duration of the study, population size, ethnicity, baseline age, baseline organ function, organ function measurements, number and frequency of measurements, any known risk factors or exposures, proportion of those exposed, average length of follow up and loss to follow up. A random sample of the extraction will also be cross-checked by a third reviewer. All the measured outcomes (functional parameters) will initially be charted to show how often they are used in studies. A group of geriatricians and primary care physicians will be recruited from Bond University and Gold Coast Hospital and Health Service. Using the modified Delphi approach, these clinicians will be asked to independently rank the organ function parameters that they deem to be the most clinically relevant marker of organ function. The survey will be performed online. The highest ranked outcomes will then be included in the data analysis.

Assessment of risk of bias in included studies

Two authors will independently appraise the quality of the included studies, using the Newcastle Ottawa Scale (NOS) for assessing risk of bias in cohort studies. Disagreements will be resolved by discussion or a third reviewer. Factors that will be assessed include:

- Representativeness of the exposed cohort
- Selection of the non-exposed cohort
- Ascertainment of exposure
- Demonstration that the outcome of interest was not present at start of study
- Comparability of cohorts on the basis of design or analysis
- Assessment of outcome
- Adequate duration of follow up

- Adequate follow up of cohorts
- Other important biases

Risk of bias for randomised controlled trials will be assessed using the Cochrane Risk of Bias tool which assesses the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessors
- Incomplete outcome data
- Selective reporting
- Other biases

Measures of treatment effect

The data will first be extracted and analysed descriptively using graphs, to determine whether it is appropriate to pool the data. If deemed appropriate, RevMan will be used to pool the data. For continuous outcomes the mean difference (MD) (or standardized mean difference if studies use different measuring scales) and corresponding 95% confidence interval (95% CI) will be calculated. The data will be extracted and reported as an annual percentage decline. The overall rates of decline and corresponding confidence intervals will be presented visually in a forest plot. If the data allow, we will also extract and stratify decade-specific decline rates. If this is not possible, then a descriptive synthesis will be presented.

Subgroup analysis

We plan to re-analyse the data by organ function parameter if more than one marker is deemed appropriate as a useful measure of a certain organ's function (e.g. location of bone mineral density measurement). We will compare decline rates of different ethnicities and sex. As well as this we will separately analyse the data of those develop disease during the course of the study and those who had known risk factors. We will also look for birth cohort effects if the data allow (i.e. cohorts who have suffered deprivation early in life may show more functional decline later in life).

Dealing with missing data

If data were missing from studies published within the last 5 years, we plan to contact authors via email to obtain the individual data set.

Assessment of heterogeneity

Statistical heterogeneity may be assessed by calculating the chi squared score, as well as the I^2 statistic. Studies will be judged to have significant heterogeneity if the P value for the chi squared test was <0.1. If using mixed models, we will report random effects as the measure of heterogeneity. The degree of heterogeneity will be determined by the I^2 as follows (as specified in the Cochrane handbook):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;

- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If there is considerable heterogeneity within the studies for the outcome, reasons for heterogeneity will be explored and results will not be pooled.

Assessment of reporting biases

If available, outcomes reported in the protocol of the studies will be judged against the final publication to assess for any reporting bias. If there are any discrepancies, these will be reported. If study protocols are not available, the outcomes listed in the methodology of the study will compared to the final reported outcomes in the results. Authors will be contacted if there are any missing data or outcomes.

Data synthesis

Where data are sufficiently similar and are thought to be clinically relevant by a group of geriatricians and primary care physicians, we will pool the study estimates of organ function. A random effects model will be used in the meta-analysis to allow for between study differences.

Sensitivity analysis

Sensitivity analyses will be conducted to check whether heterogeneity in the overall outcomes can be explained by either of the following:

- the presence of low quality studies with high risk of bias (assessed as having one or more domains with a high risk of bias according to the NOS).
- duration of the study or time-points of measurement

DISCUSSION

This review aims to provide an estimate of annual organ function decline across various organs that is part of normal aging in people without symptomatic disease. This will enable clinicians to distinguish age-appropriate laboratory test results from values which represent increased risk of disease. It is more reasonable to assess the health of individuals with reference to others in their age cohorts, not in comparison to healthy young individuals. Determining these 'normal' changes with aging will also avoid the psychological consequences of disease-labelling and side effects of unnecessary drug treatment. Researchers will be able to use this data to plan more longitudinal studies in different cohorts and investigate additional factors that affect changes in organ function. Further research will also be required to determine whether it is possible to regain function and if so, up until what point this is possible once a risk factor is removed.

ABBREVIATIONS

FEV_1 – Forced expiratory volume in 1 second
eGFR - estimated glomerular filtration rate
NOS- Newcastle Ottawa Scale

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

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AUTHORS' CONTRIBUTIONS

ETT, SS and PG were involved in the conception and design of the review. ETT developed the search strategy. ETT drafted the manuscript, and MG, SS, KB and PG contributed to the drafting of the review protocol. All authors approved the final version of the article.

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PUBMED SEARCH STRATEGY

1. ("forced expiratory volume"[tiab] OR FEV[tiab] OR "forced vital capacity"[tiab] OR FVC[tiab] OR spirometry[Mesh] OR spirometry[tiab] OR "lung function"[tiab] OR "pulmonary function"[tiab] OR "Expiratory Flow"[tiab])
   AND
2. ("Aging/ethnology"[Mesh] OR "Aging/physiology"[Mesh] OR “Age-related”[tiab] OR “Age related”[tiab] OR Function[tiab] OR Healthy[tiab])
   AND
3. (Decline[tiab] OR Declines[tiab] OR Declined[tiab] OR Decrease[tiab] OR Decreased[tiab])
   AND
4. ("Middle Aged"[Mesh] OR "Aged"[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Old[tiab] OR Older[tiab])
   AND
5. ("Longitudinal Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR Longitudinal[tiab] OR Trend[tiab] OR Trends[tiab] OR Trajectories[tiab] OR Trajectory[tiab] OR “Follow-up”[tiab] OR “Follow up”[tiab] OR “Rate of”[tiab] OR “Rates of”[tiab])
   AND
6. (Cohort[tiab] OR Observational[tiab] OR Prospective[tiab] OR Compared[tiab] OR Investigated[tiab] OR Evaluating[tiab] OR Analysis[tiab] OR Analyzed[tiab] OR Statistics[tiab] OR Data[tiab] OR Baseline[tiab])
   AND
7. (Humans[Mesh] OR Humans[tiab] OR Human[tiab] OR Population[tiab])

REFERENCES

1. Mathers C, Stevens G, Mahanani W, Ho J, Fat D, Hogan D. WHO methods and data sources for country-level causes of death 2000-2015. Geneva: Department of Information, Evidence and Research WHO; 2017.
2. Boss G, Seegmiller J. Age-Related Physiological Changes and their Clinical Significance. West J Med 1981;135:434-40.
3. Aalami O, Fang T, Song H, Nacamuli R. Physiological Features of Aging Persons. Arch Surg 2003;138:1068-76.
4. Rodríguez-Rodero S, Fernández-Morera J, Menéndez-Torre E, Calvanese V, Fernández A, Fraga M. Aging Genetics and Aging. Aging and Disease 2011;2:186-95. .
5. Vásárhelyi B, Debreczeni L. Lab test findings in the elderly. J Int Fed Clin Chem 2017;28:328-32.
6. Navaratnarajah A, Jackson S. The physiology of ageing. Medicine 2017;45:6-10.
7. Knudson R, Lebowitz M, Holberg C, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983;127:725-34.
8. Zaugg M, Lucchinetti E. Respiratory Function in the Elderly. Anesthesiol Clin North America 2000;18:47-58.
9. Vestal R, McGuire E, Tobin J, al e. Aging and ethanol metabolism Clin Pharmacol Ther 1977;21:343-54.
10. Adkins R, Marshall B. Anatomic and physiologic aspects of aging.
. In: Adkins R, Scott H, eds. Surgical Care for the Elderly. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998:xxi531.
11. Van Tongeren J, Cluysenaer O, Lamers C, De Mulder P, Yap S. Causes of hypoalbuminemia. In: Yap S, Majoor C, van Tongeren J, eds. Clinical Aspects of Albumin. Dordrecht: Springer; 1978.
12. George J, Byth K, Farrell G. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. . Biochem Pharmacol 1995;50:727-30.
13. Loi C, Parker B, Cusack B, Vestal R. Aging and drug interactions. III. Individual and combined effects of cimetidine and cimetidine and ciprofloxacin on theophylline metabolism in healthy male and female nonsmokers. J Pharmacol Exp Ther 1997;280:627-37.
14. McConnell J, Buchanan K, Ardill J, Stout R. Glucose tolerance in the elderly: the role of insulin and its receptor. Eur J Clin Invest 1982;12:55-61.
15. Meigs J, Muller D, Nathan D, Blake D, R A. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003;52:1475-84.
16. Pathy J, Sinclair A, Morley J, Vellas B. Pathy's Principles and Practice of Geriatric Medicine. Oxford: UK: John Wiley & Sons, Ltd; 2012.
17. Levey A, Stevens L, Coresh J. Conceptual model of CKD: applications and implications. Am J Kidney Dis 2009;53:S4-16.
18. Stevens L, Viswanathan G, Weiner D. CKD and ESRD in the Elderly: Current Prevalence, Future Projections and Clinical Significance. Adv Chronic Kidney Dis 2010;17:293-301.
19. Moynihan R, Glassock R, Doust J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased. BMJ 2013;347:f4298.