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The Association Between Physical Function and Hyperkyphosis in Older Females: Protocol for a Systematic Review

Abstract

Identifying factors that impact physical function in older populations is important for the maintenance of good health with aging. Age-related hyperkyphosis, an excessive curvature in the thoracic spine, affects up to 40% of the older adults and is more common in older females than males. An association of age-related hyperkyphosis with impaired physical function has been reported in numerous studies, however, other studies have reported that a greater magnitude of kyphosis did not associate with impaired physical function. Given the inconsistencies regarding the impact of hyperkyphosis on physical function, the purpose of our study is to perform a systematic review of the existing studies in order to better describe the association between hyperkyphosis and physical function. Prospective and retrospective cohort, case-control, and cross-sectional studies which measure physical function by valid functional tests and questionnaires in older females will be included. We will search Scopus, ISI Web of Science, Cochrane Library, PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PEDro databases. Studies will be searched and then selected by two independent reviewers based on quality assessment tools from the National Heart, Lung, and Blood Institute (NHLBI). A meta-analysis will be conducted if data reported for individual studies allow. Specifically, if two or more individual studies provide measures of central tendency and variability from any of the categories of physical function measures, data will be gathered for meta-analysis. If a meta-analysis is not possible, data will be synthesized and described in a narrative form by size and variability of effect, direction of effect, and association with hyperkyphosis.

Keywords: Aged, female, kyphosis, physical functional performance

Introduction

One of the challenges facing the older population is the maintenance of physical function, which is an important prerequisite for the performance of basic (self-care and walking) and instrumental (home management and community mobility) activities of daily living (ADLs). Physical function and ADL performance are important both for the participation in social, vocational, recreational activities^[1] and also to prevent limitations in the activities of daily living and disability in older adults.^[2] Therefore, attention to factors contributing to the loss of physical function is important when developing standards of health care and prevention in the older populations.

The aging process alters normal postural alignment.^[3] Among age-related postural changes, a common clinical finding is an excessive thoracic kyphosis curvature

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which affects 20-40% of older adults above 60 years of age.^[4] Aging can lead to a decrease in the efficiency of the nervous system,^[5,6] skeletal mass (osteoporosis),^[7] muscle mass and function (sarcopenia),^[8] with a concurrent gradual increase in the fragility of the connective tissue.^[9] These physiological changes are known contributors to increasing kyphosis.^[9] While there is no accepted threshold differentiating normal from abnormally increased kyphosis angle, a kyphosis angle greater than 40° is often used to define hyperkyphosis.[10,11] Females may be at higher risk of hyperkyphosis due to hormone changes with menopause and other sex-related factors such as poor spinal extensor muscle quality,^[12] low spinal muscle strength^[13] and endurance,^[14] low bone mineral density, vertebral fractures,[15] and the weight of hanging breasts.^[10] Once kyphosis reaches 50°, the risk for falls^[16,17] and fractures increases,^[18] either of which can have devastating consequences in reducing the physical function. Therefore,

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the prevention of progression of thoracic kyphosis with aging may be a preventive strategy to reduce the adverse health outcomes of hyperkyphosis such as falls, bone fractures, and declines in ADL.^[19]

Numerous cross-sectional and longitudinal studies have associated age-related hyperkyphosis with impaired physical function,^[20-25] but contradictory evidence indicates that hyperkyphosis may not be linked to impaired function.^[26-28] Physical function limitations associated with hyperkyphosis in older adults have included reduced gait speed, decreased stair-climbing speed, reduced functional reach,[20,29] lower chair stand test scores,^[20,21,24] lower grip strength,^[20,24] and poor balance.^[30] In contrast, using supine computed tomography scans to measure thoracic Cobb angle of kyphosis in older adults (mean age 61 ± 8 years, range 50–85), Lorberg *et al.*^[26] reported that the walking speed, grip strength, chair stand time, and frequency of self-reported physical impairment did not differ between individuals in the highest and lowest quartile of kyphosis; furthermore, a greater magnitude of kyphosis did not predict physical function over a mean of 3.4 years. Moreover, others also reported^[27] no association between kyphosis and lower-extremity physical function, but did attribute loss of trunk extensor muscle endurance with a decline in the lower-extremity function over time. The link between hyperkyphosis and physical function is further questioned by the lack of evidence for improved physical function in randomized controlled trials that report improved kyphosis.[31-34]

Given these inconsistencies regarding the association between hyperkyphosis and physical function in older females, the impact of hyperkyphosis on physical function is not clearly known. There is a need for further studies, especially in older females who may exhibit a higher degree of kyphosis, to investigate whether age-related hyperkyphosis is a risk factor for impaired physical function. The primary aim of this study is to systematically review the existing studies and describe the association between hyperkyphosis and physical function in older females. The secondary aim is to assess the physical function in older females with hyperkyphosis compared to normative data for older females without hyperkyphosis.

Methods and Analysis

The Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) guides the preparation and reporting of this protocol for the systematic review.^[35] The PRISMA Flow Diagram will be used to describe the flow of information through the different phases of this systematic review.^[36]

Eligibility criteria

Study designs

We will include prospective and retrospective cohort studies, case-control studies, and cross-sectional studies.

We will exclude qualitative studies, case reports, case series, ecological studies, and reviews.

Participants

Studies involving females aged 60 years and older will be included.^[37] We will consider studies addressing both older females and older males if data provided for older females are reported separately. We will exclude studies that include males only.

Exposure

We will include studies involving females with thoracic hyperkyphosis. It will be defined as an angle of thoracic curvature greater than 40° using radiographic image or devices such as the Spinal Mouse, Kyphometer, Goniometer, Inclinometer, or Flexi Curve Ruler. If the mean baseline angle of kyphosis is not given, inclusion will be on the basis of having a flexed posture, a flexible ruler kyphosis index >13°,^[38] occiput to the wall >5 cm^[39,40] and a block method result of ≥3 blocks^[41] at the baseline. We will consider both manuscripts with two group comparisons (hyperkyphosis, normal kyphosis) and those with one group describing the association between hyperkyphosis and physical function.

Outcomes

The outcomes of interest are physical function measures used in older females with hyperkyphosis. Physical function should be measured and reported by valid functional tests and questionnaires. Studies that do not use valid functional tests and questionnaires will be excluded.

Timing

For cohort studies, follow-up time should be at least 1 year.

Setting

There will be no restrictions by the type of setting.

Language

We will include articles reported in the English language. Studies in non-English language will be excluded.

Access to the full text

The full text of the article should be provided. If the full text of any article is unavailable, authors will correspond with the author/authors of the article or the editor of the publishing journal at least three times.

Information sources

A comprehensive search strategy will be elaborated with the help of an experienced librarian according to the Medical Subject Headings (MESHs) and text words related to the concepts of kyphosis, function, and females aged ≥ 60 years. Scopus, ISI Web of Science, Cochrane Library, PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and PEDro databases will be searched by two reviewers. All available data will be used through the time of the last search.

To ensure literature saturation, we will scan the reference lists of included studies or relevant reviews identified through the search. When the full version of the article is not found, the researcher will communicate a maximum of three times with the corresponding author/authors or editor of the journal in an attempt to access the article. To find Gray literature, specialized resources and other resources will be investigated, e.g., http://www.gateway. com/worldwide/,•http://www.proquest.com/.

Search strategy

No study design, date, or language limits will be imposed on the search. A comprehensive search strategy will be created by an experienced librarian, then this strategy will be developed with input from the project team. Finally, the strategy will be reviewed by one of the authors (with expertise in systematic review searching). The key terms will be updated during the research process, and the search will be repeated with the related articles' key terms. The reference lists of relevant articles will be examined for additional eligible studies (Hand or Recursive Search).

MESH terms and keywords associated with older female adults, hyperkyphosis, and physical function were used to design the search strategy [Table 1].

Selection process

Two independent reviewers will be involved in the study selection. The study selection process is summarized in the PRISMA flow diagram [Figure 1].

Data management

Related articles will be extracted from each database. The iInitial search results from all databases will be screened for duplicates using EndNote (X5 (Bld 5478), Thomson Reuters). Two authors will independently screen titles and/or abstracts of all identified studies that potentially meet the inclusion criteria and those from the additional sources will be screened independently. Unrelated studies will be eliminated. Review studies will not be included in the final analysis. However, their references will be considered by the method of Cross Reference. The key terms will be updated during the research process: they will be repeated with the related articles' key terms and the search will be repeated.

The total number of articles will be determined, articles from each database will be reported, and the process will be described in the PRISMA diagram.

Data collection process

The full text of each article identified for inclusion in the systematic review will be read and the relevant data will be extracted using a standardized data extraction form. Following the PRISMA guidelines, two authors will extract data independently and in duplicate from each eligible study. Reviewers will resolve disagreements by discussion and a third researcher will adjudicate unresolved disagreements. Information not currently available within the studies will be requested directly from the authors via email.

Data items:

The following data will be extracted from each included study:

Table 1: Draft PubMed search		
Population	Exposure	Outcome
Female	Kyphosis	"Physical function"
Woman	Kyphoses	"Physical Functional Performance"
Women	Hyperkyphosis	"Functional Performance"
"Older Adult"	Kyphotic	"Physical Performance"
"Older Women"	"Flexed posture"	mobility
"Older People"	"kyphotic posture"	"mobility limitation"
"Frail Older Adults"	Posture	Ambulation
Aging	Flexed	Walking
Aged	Trunk	Gait
Elderly	Spinal	"Lower Extremity"
Seniors	(23 OR 25 OR 26) AND (17 OR 18 OR 19 OR 20 OR 24) 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27	"Physical Functional Impairment"
"In Old Age"		29 OR 30 OR 31 OR 32 OR
Older		33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39
Senile		
(1 OR 2 OR 3) AND (8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14)	23 OK 20 OK 27	
1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15		

Final search (#41): 16 AND 28 AND 40

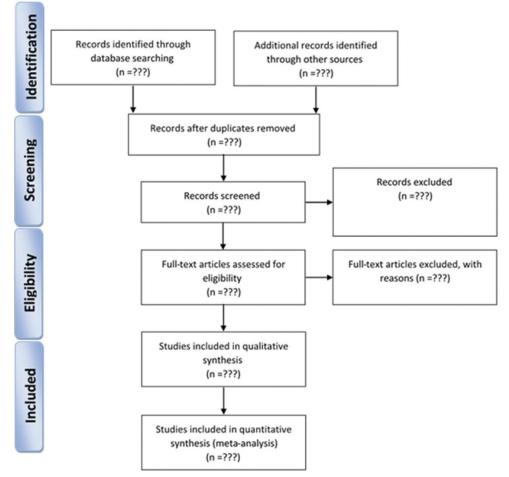


Figure 1: Flow diagram of the study selection process based on the PRISMA guideline

- 1. Overall study characteristics (including first author, year of publication, language)
- 2. Characteristics of participants (age and gender)
- 3. Information on study design (type of study, number of participants)
- 4. Exposure details (method of measuring kyphosis, kyphosis angle, and control group)
- 5. Outcome measures (method of measuring physical function, objective tests, and subjective questionnaires)
- 6. Main findings.

Primary outcome

The primary outcomes of interest will include objective measurements (with different parameters including time, distance, speed, and strength), subjective questionnaire (i.e., NEADLI, LLFDI (Nottingham Extended Activities of Daily Living Index, Late-Life Function and Disability Instrument)) or self-reported functional status (i.e., using the 1984 Health Interview Survey Supplement on Aging instrument).

Quality of (risk of bias in) individual studies

We will use quality assessment tools from the National Heart, Lung, and Blood Institute (NHLBI). Selection of the

checklist will be based on the study design. We will use one tool for observational cohort and cross-sectional studies, and another tool for case-control studies.^[42] These tools focus on key concepts for critical appraisal of the internal validity of a study. The tools do not provide a list of factors comprising a numeric score. The items of the tools evaluate potential flaws in study methods or implementation including sources of bias, confounding, study power, and other factors.^[43]

Two authors will apply and evaluate the items of the tools first separately, and then, together. They will select "yes," "no" or "cannot determine (CD)/not reported (NR)/ not applicable (NA) " in response to each item in the tool, and judge each study as "good, " "fair" or "poor."^[43] Disagreements will be resolved based on the third researcher's opinion who supervises the results.

Quality score is the number of items from the checklist addressed as a percentage of the total number of items applicable. Studies with a quality assessment below 50% will be excluded.

Confidence in cumulative evidence

After reviewing all the evidence and assessing the risk of bias according to the NHLBI checklists, we will grade confidence in the cumulative evidence using the levels of evidence on the A, B, C scale recommended by the American Heart Association.^[44]

Data synthesis

A meta-analysis will be conducted if data reported for individual studies allow. Specifically, if two or more individual studies provide measures of central tendency and variability (for aggregation using Cohen's d standardized response mean) or frequency of association with kyphosis (for aggregation using odds ratios: OR) from any of the categories of physical function measures-objective measures, subjective questionnaires, or self-reported functional status-data will be gathered for meta-analysis. Data will be collected for those with and without hyperkyphosis. Individual article effect sizes (d or OR) will be calculated with 95% confidence intervals comparing physical functioning between those with and without hyperkyphosis. Individual article effect sizes will be weighted by inverse variance and averaged using a fixed effect or random effects model depending on the size of the heterogeneity Q statistic. If the P value for the Q statistic is less than 0.05, then a random effects model will be used. The meta-analysis for each category of physical function measure is expected to support or refute the hypothesis that hyperkyphosis is related to physical function in older women.

If a meta-analysis is not possible, data will be synthesized and described in a narrative form by size and variability of the effect, direction of effect, and relationship with hyperkyphosis.

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Conflicts of interest

There are no conflicts of interest.

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References

- Painter P, Stewart AL, Carey S. Physical functioning: Definitions, measurement, and expectations. Adv Ren Replace Ther 1999;6:110-23.
- Ishiyama D, Yamada M, Nishio N, Shinohara A, Kinkawa J, Teruya K, *et al.* Factors associated with low physical performance among older inpatients. J Clin Gerontol Geriatr 2018;9:13-9.
- Benvenuti F. Physiology of human balance. Adv Neurol 2001;87:41-51.
- Kado DM, Huang MH, Karlamangla AS, Barrett-Connor E, Greendale GA. Hyperkyphotic posture predicts mortality in older community-dwelling men and women: A prospective study. J Am Geriatr Soc 2004;52:1662-7.
- 5. Papegaaij S, Taube W, Baudry S, Otten E, Hortobagyi T. Aging causes a reorganization of cortical and spinal control of posture.

Front Aging Neurosci 2014;6:28.

- Aagaard P, Suetta C, Caserotti P, Magnusson SP, Kjaer M. Role of the nervous system in sarcopenia and muscle atrophy with aging: Strength training as a countermeasure. Scand J Med Sci Sports 2010;20:49-64.
- Hemmatian H, Bakker AD, Klein-Nulend J, van Lenthe GH. Aging, osteocytes, and mechanotransduction. Curr Osteoporos Rep 2017;15:401-11.
- Marty E, Liu Y, Samuel A, Or O, Lane J. A review of sarcopenia: Enhancing awareness of an increasingly prevalent disease. Bone 2017;105:276-86.
- Drzal-Grabiec J, Snela S, Rykala J, Podgorska J, Banas A. Changes in the body posture of women occurring with age. BMC Geriatr 2013;13:108.
- 10. Fon GT, Pitt MJ, Thies AC Jr. Thoracic kyphosis: Range in normal subjects. AJR Am J Roentgenol 1980;134:979-83.
- 11. Voutsinas SA, MacEwen GD. Sagittal profiles of the spine. Clin Orthop Relat Res 1986;210.
- Anderson DE, D'Agostino JM, Bruno AG, Demissie S, Kiel DP, Bouxsein ML. Variations of CT-based trunk muscle attenuation by age, sex, and specific muscle. J Gerontol A Biol Sci Med Sci 2013;68:317-23.
- 13. Kamel HK. Sarcopenia and aging. Nutr Rev 2003;61:157-67.
- Roghani T, Khalkhali Zavieh M, Talebian S, Akbarzadeh Baghban A, Katzman W. Back muscle function in older women with age-related hyperkyphosis: A comparative study. J Manipulative Physiol Ther 2019;42:284-94.
- Van der Klift M, De Laet CE, McCloskey EV, Hofman A, Pols HA. The incidence of vertebral fractures in men and women: The Rotterdam Study. J Bone Miner Res 2002;17:1051-6.
- McDaniels-Davidson C, Davis A, Wing D, Macera C, Lindsay SP, Schousboe JT, *et al.* Kyphosis and incident falls among community-dwelling older adults. Osteoporos Int 2018;29:163-9.
- van der Jagt-Willems HC, de Groot MH, van Campen JP, Lamoth CJ, Lems WF. Associations between vertebral fractures, increased thoracic kyphosis, a flexed posture and falls in older adults: A prospective cohort study. BMC Geriatr 2015;15:34.
- Kado DM, Miller-Martinez D, Lui LY, Cawthon P, Katzman WB, Hillier TA, *et al.* Hyperkyphosis, kyphosis progression, and risk of non-spine fractures in older community dwelling women: The study of osteoporotic fractures (SOF). J Bone Miner Res 2014;29:2210-6.
- Sugai K, Michikawa T, Takebayashi T, Nishiwaki Y. Association between muscle strength, mobility, and the progression of hyperkyphosis in the elderly: The Kurabuchi cohort study. J Gerontol A Biol Sci Med Sci 2019;12:1987-92.
- 20. Kado DM, Huang MH, Barrett-Connor E, Greendale GA. Hyperkyphotic posture and poor physical functional ability in older community-dwelling men and women: The Rancho Bernardo study. J Gerontol A Biol Sci Med Sci 2005;60:633-7.
- Antonelli-Incalzi R, Pedone C, Cesari M, Di Iorio A, Bandinelli S, Ferrucci L. Relationship between the occiput-wall distance and physical performance in the elderly: A cross sectional study. Aging Clin Exp Res 2007;19:207-12.
- 22. Katzman WB, Vittinghoff E, Kado DM. Age-related hyperkyphosis, independent of spinal osteoporosis, is associated with impaired mobility in older community-dwelling women. Osteoporos Int 2011;22:85-90.
- Katzman WB, Vittinghoff E, Ensrud K, Black DM, Kado DM. Increasing kyphosis predicts worsening mobility in older community-dwelling women: A prospective cohort study. J Am Geriatr Soc 2011;59:96-100.

- 24. Katzman WB, Huang MH, Lane NE, Ensrud KE, Kado DM. Kyphosis and decline in physical function over 15 years in older community-dwelling women: The Study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2013;68:976-83.
- Eum R, Leveille SG, Kiely DK, Kiel DP, Samelson EJ, Bean JF. Is kyphosis related to mobility, balance, and disability? Am J Phys Med Rehabil 2013;92:980-9.
- Lorbergs AL, Murabito JM, Jarraya M, Guermazi A, Allaire BT, Yang L, *et al.* Thoracic kyphosis and physical function: The Framingham study. J Am Geriatr Soc 2017;65:2257-64.
- 27. Ward RE, Beauchamp MK, Latham NK, Leveille SG, Percac-Lima S, Kurlinski L, *et al.* Neuromuscular impairments contributing to persistently poor and declining lower-extremity mobility among older adults: New findings informing geriatric rehabilitation. Arch Phys Med Rehabil 2016;97:1316-22.
- Eagan MS, Sedlock DA. Kyphosis in active and sedentary postmenopausal women. Med Sci Sports Exerc 2001;33:688-95.
- Hirose D, Ishida K, Nagano Y, Takahashi T, Yamamoto H. Posture of the trunk in the sagittal plane is associated with gait in community-dwelling elderly population. Clin Biomech 2004;19:57-63.
- Lynn SG, Sinaki M, Westerlind KC. Balance characteristics of persons with osteoporosis. Arch Phys Med Rehabil 1997;78:273-7.
- Pawlowsky SB, Hamel KA, Katzman WB. Stability of kyphosis, strength, and physical performance gains 1 year after a group exercise program in community-dwelling hyperkyphotic older women. Arch Phys Med Rehabil 2009;90:358-61.
- 32. Katzman WB, Sellmeyer DE, Stewart AL, Wanek L, Hamel KA. Changes in flexed posture, musculoskeletal impairments, and physical performance after group exercise in community-dwelling older women. Arch Phys Med Rehabil 2007;88:192-9.
- Greendale GA, McDivit A, Carpenter A, Seeger L, Huang MH. Yoga for women with hyperkyphosis: Results of a pilot study. Am J Public Health 2002;92:1611-4.
- 34. Katzman WB, Parimi N, Gladin A, Poltavskiy EA, Schafer AL, Long RK, *et al.* Sex differences in response to targeted kyphosis specific exercise and posture training in community-dwelling older adults: A randomized controlled trial. BMC Musculoskelet

Disord 2017;18:509.

- Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: Elaboration and explanation. BMJ 2015;349:g7647. doi: https:// doi.org/10.1136/bmj.g7647.
- 36. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. J Clin Epidemiol 2009;62:e1-34.
- World Health Organization. Ageing and health 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/ ageing-and-health. [Last accessed on 2018 Feb 05].
- Kado DM, Prenovost K, Crandall C. Narrative review: Hyperkyphosis in older persons. Ann Intern Med 2007;147:330-8.
- Bansal S, Katzman WB, Giangregorio LM. Exercise for improving age-related hyperkyphotic posture: A systematic review. Arch Phys Med Rehabil 2014;95:129-40.
- Balzini L, Vannucchi L, Benvenuti F, Benucci M, Monni M, Cappozzo A, *et al.* Clinical characteristics of flexed posture in elderly women. J Am Geriatr Soc 2003;51:1419-26.
- 41. Yokoyama Y, Nishiwaki Y, Michikawa T, Imamura H, Nakamura T, Takebayashi T, *et al.* The association of kyphosis assessed in supine and standing positions with future activities of daily living dependence: The Kurabuchi Study. Arch Osteoporos 2017;12:105.
- National Heart Lung and Blood Institute. Study Quality Assessment Tools 2013. https://www.nhlbi.nih.gov/health-topics/ assessing-cardiovascular-risk. [Last accessed on 2022 Feb 20].
- 43. National Heart Lung and Blood Institute (NHLBI). Assessing cardiovascular risk: Systematic evidence review from the risk assessment work group 2013. Available from: https://www.nhlbi. nih.gov/health-topics/assessing-cardiovascular-risk.
- 44. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, *et al.* Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016;47:e98-169. doi: 10.1161/ STR.0000000000000098.