PHILIPPINE GUIDELINES on PERIODIC HEALTH EXAMINATION (Phase 3)

Task Force on Renal, Metabolic, Nutrition, and Endocrine Disorders

PERIODIC HEALTH EXAMINATION TASK FORCE 2022-2023

Submitted 10 August 2023

Disclaimer and Contact Information

This guideline is intended to be used by general practitioners, specialists, allied health professionals who are primary care providers. Although adherence to this guideline is encouraged by the DOH, it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history and current physical status dictate and while their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this guideline should not also be treated as strict rules on which to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence as of the time of its formulation. However, certain aspects of the screening may not have been addressed by the clinical trials and observational studies, and as such, evidence bases are therefore not all inclusive. Considerations on these aspects were still deemed necessary in the current contexts of primary care.

Contact Us

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The Task Force members undertook extensive technical work in (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel discussion, and documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups, and committees, and facilitating the *en banc* meeting. The CPG Central Steering Committee and the Task Force Steering Committee were responsible for overall organization and management and were accountable for the quality of the CPG.

Lastly, this guideline was completed through the invaluable contribution and participation of panelists from different sectors of healthcare who committed their time and effort, Their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences were crucial in formulating the recommendations.

We thank all in contributing to this endeavor.

How to cite:

Participating Societies, Organizations, Agencies and/or Institutions

Association of Municipal Health Officers of the Philippines (AHMOP)

Food and Nutrition Research Institute, Department of Science and Technology (DOST-FNRI)

Philippine Academy of Family Physicians (PAFP)

Philippine Alliance of Patient Organizations (PAPO)

Philippine Association of Nutrition (PAN)

Philippine College of Endocrinology, Diabetes, and Metabolism (PCEDM)

Philippine College of Physicians (PCP)

Philippine Society of Nephrology (PSN)

List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin-converting enzyme
ACP	American College of Physicians
AER	Albumin excretion rate
AHA	American Heart Association
AHMOP	Association of Municipal Health Officers of the Philippines
AMH	Anti-müllerian hormone
AMI	Acute myocardial infarction
aOR	Adjusted odds ratio
aPR	Adjusted prevalence ratio
ASEAN	Association of Southeast Asian Nations
BMD	Bone mineral density
BMI	Body mass index
CBC	Complete blood count
CEE	Conjugated equine estrogen
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CPG	Clinical practice guideline
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CQ	Clinical question
CV	Cardiovascular
CVD	Cardiovascular disease
DOH	Department of Health
DOST-FNRI	Department of Science and Technology Food and Nutrition Research Institute
DVT	Deep venous thrombosis
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EtD	Evidence-to-decision
FPG	Fasting plasma glucose
FSH	Follicle-stimulating hormone
GDP	Gross domestic product
GFR	Glomerular filtration rate
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HbA_{1C}	Hemoglobin A1C
HR	Hazards ratio
HRT	Hormone replacement therapy
iCa	Ionized calcium
ICC	Intraclass correlation coefficient
IDA	Iron deficiency anemia
IGFBP-3	Insulin-like growth factor-binding protein 3
IGF-1	Insulin-like growth factor 1

IPDMA	Individual participant data meta-analysis
LH	Luteinizing hormone
LMICs	Low- and middle-income countries
MACE	Major adverse cardiovascular events
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Headings
MUAC	Mid-upper arm circumference
NCR	National Capital Region
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Care Excellence
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAFP	Philippine Academy of Family Physicians
PAN	Philippine Association of Nutrition
PAPO	Philippine Alliance of Patient Organizations
PCEDM	Philippine College of Endocrinology, Diabetes, and Metabolism
PCP	Philippine College of Physicians
PHEX	Philippine Guidelines on Periodic Health Examination
PHIC	Philippine Health Insurance Corporation
PICO	Population, intervention, comparison, outcome
POGS	Philippine Obstetrical and Gynecological Society
PREVEND	Prevention of Renal and Vascular Endstage Disease
PSN	Philippine Society of Nephrology
QALY	Quality-adjusted life-years
RBC	Red blood cell
RCTs	Randomized controlled trial
RevMan	ReviewManager
RHU/HC	Rural health unit/health center
ROC AUC	Receiver-operating characteristic area under the curve
RR	Relative risk
SC	Steering committee
Sn	Sensitivity
Sp	Specificity
SRMA	Systematic review and meta-analysis
TOS	The Obesity Society
T2DM	Type 2 diabetes mellitus
UAC	Urine albumin concentration
UACR	Urine albumin-to-creatinine ratio
UK	United Kingdom
ULT	Urate-lowering therapy
US	United States
VMS	Vasomotor symptoms
VVS	Vasovagal syncope
WC	Waist circumference
WHI	Women’s Health Initiative
WHR	Waist-hip ratio

WHtR Waist-height ratio

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Executive Summary

This Clinical Practice Guideline for the Periodic Health Examination (Renal, Metabolic, Nutrition, and Endocrine) is an output from the joint undertaking of the Department of Health and National Institutes of Health- Institute of Clinical Epidemiology.

This clinical practice guideline is a systematic synthesis of evidence to address screening for high climacteric syndrome, hypocalcemia or hypercalcemia, prediabetes, chronic kidney disease, hyperuricemia, malnutrition, nutritional anemia, among asymptomatic, apparently healthy adult Filipinos, and sexual maturity among asymptomatic, apparently healthy adolescent Filipinos. The CPG provided eighteen (18) recommendations on prioritized questions in the screening for certain disease conditions.

Recommendations are based on the appraisal of the best available evidence on each of the eight identified clinical questions. The CPG is intended to be used by general practitioners and specialists in the primary care setting, policy makers, employers and administrators, allied health practitioners and even patients. The guideline development process followed the widely accepted Grading of Recommendations, Assessment, Development, and Evaluation or the GRADE approach including GRADE Adolopment[1], a systematic process of adapting evidence summaries and the GRADE Evidence to Decision or EtD framework[2]. It included 1) identification of critical questions and critical outcomes, 2) retrieval of current evidence, 3) assessment and synthesis of the evidence base for these critical questions, 4) formulation of draft recommendations, 5) convening of a multi-sectoral stakeholder panel to discuss values and preferences and assess the strength of the recommendations, and 6) planning for dissemination, implementation, impact evaluation and updating.

The recommendations in this CPG shall hold and will be updated after 3 years or when new evidence arise.

Summary of Recommendations

Recommendation	Certainty of Evidence	Strength of Panel Recommendation
Question 1. Should screening for high risk climacteric syndrome be done among apparently, healthy asymptomatic women?		
1.1. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest against routine screening for high climacteric syndrome using follicle-stimulating hormone (FSH).	Low	Weak
1.2. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest against routine screening for high climacteric syndrome using luteinizing hormone (LH).	Low	Weak
1.3. Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest against routine screening for high climacteric syndrome using estradiol.	Low	Weak
Question 2. Should screening for hypocalcemia or hypercalcemia be done among apparently healthy, asymptomatic adults?		
2.1. Among apparently healthy asymptomatic adults, we recommend against routine screening for hypocalcemia or hypercalcemia using serum calcium.	Low	Strong
2.2. Among apparently healthy, asymptomatic adults, we recommend against routine screening for hypocalcemia or hypercalcemia using electrocardiogram (ECG).	Low	Strong
2.3. Among apparently healthy, asymptomatic adults, we recommend against routine screening for hypocalcemia or hypercalcemia using bone mineral density (BMD).	Low	Strong

Question 3. Should screening for prediabetes be done among apparently healthy, asymptomatic individuals?		
3.1. Among apparently healthy, asymptomatic adults aged 40 years above, or younger if with risk factors, we recommend screening for prediabetes and type 2 diabetes mellitus using fasting plasma glucose.	Moderate	Strong
3.2. Among apparently healthy, asymptomatic adults aged 40 years above or, younger if with risk factors, we suggest screening for prediabetes and type 2 diabetes mellitus using hemoglobin A_{1C}.	Moderate	Weak
Question 4. Should screening for chronic kidney disease be done among apparently healthy, asymptomatic adults?		
4.1. Among apparently healthy, asymptomatic adults, we suggest against routine screening for chronic kidney disease (CKD) using estimated glomerular filtration rate (eGFR) computed with CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation.	Low	Weak
4.2. Among apparently healthy, asymptomatic adults, we suggest against routine screening for CKD using urine albumin creatinine ratio (UACR) or urine albumin concentration (UAC).	Low	Weak
4.3. Among apparently healthy, asymptomatic adults, we suggest against routine screening for CKD using kidney ultrasonography.	Low	Weak
Question 5. Should screening for hyperuricemia be done among apparently healthy asymptomatic individuals?		
5. Among apparently healthy asymptomatic adults, we recommend against routine screening for hyperuricemia using serum uric acid.	Low	Strong
Question 6. Should screening for malnutrition be done among apparently, healthy asymptomatic adults?		

6.1. Among apparently healthy, asymptomatic adults, we suggest screening for central obesity using waist circumference.	Low	Weak
6.2. Among apparently healthy asymptomatic adults, we suggest screening for central obesity using waist-hip ratio.	Low	Weak
6.3. Among apparently healthy, asymptomatic adults, we suggest against screening for malnutrition using mid-upper arm circumference.	Low	Weak
6.4. Among apparently healthy, asymptomatic adults, we recommend routine screening for obesity using body mass index.	Low	Strong
Question 7. Should screening for nutritional anemia be done among apparently healthy, asymptomatic adults?		
7. Among apparently healthy, asymptomatic adults, we recommend screening for nutritional anemia using hemoglobin and red blood cell (RBC) parameters.	Low	Strong
Question 8. Should screening for sexual maturity be done among apparently healthy, asymptomatic adolescents?		
8. Among asymptomatic adolescents, we suggest against routine assessment of sexual maturity using Tanner Staging.	Low	Weak

1. Introduction

The Philippine Guidelines on Periodic Health Examination (PHEX) was first published in 2004. It was a comprehensive appraisal and synthesis of evidence on screening interventions committed to providing early prevention services among apparently healthy Filipinos. It was a long-awaited publication and the first to offer evidence-based recommendations for screening tests made possible through the concerted effort of various medical and paramedical organizations composed of more than a hundred experts, researchers, and stakeholders.[3] It was inspired by the Canadian and the US Preventive Services Task Forces, but it was tailored to the Philippine setting.

Due to the evolving technology, scientific evidence, and health policies, there is a pressing need to update this guideline. This 2023 Philippine Guidelines will support the objectives stated in the Universal Health Care Act that all Filipinos are given access to quality and affordable medical services, including primary care benefits.[4, 5]

In the guideline development, evidence-based recommendations for the prioritized health screening were formulated using the GRADE Evidence-to-Decision (EtD) framework.[1, 6] The EtD framework aims to facilitate the adaptation of recommendations and decisions of experts and stakeholders based on specific contexts, essential health outcomes, benefits, and harms while looking through the equity, applicability, and feasibility lenses.

The evidence collated to answer the research questions on screening tests are used in formulating the recommendations. They can be classified into two: (1) screening for a risk factor and (2) screening for early disease. Screening for the former is directed towards determining the effective management of the condition as a risk factor, and screening for the latter is focused on the performance of the tests that will be used to detect and subsequently treat that early disease and prevent it from progressing.

Health screening also carries potential harm, for example, mislabeling the person as being ill. It can pose a threat to the psychological, social, or physical well-being and even to the individual's financial stability. Because of these probable adverse effects of screening, criteria are set to determine if screening for a particular condition can be beneficial and pragmatic. The voting panel members used these criteria (5) aligned with the EtD framework: (1) burden of illness must be high, (2) screening tests must be accurate enough, (3) early treatment must be more effective than late treatment, (4) confirmatory tests and early management must be safe and available, and (5) costs of screening must be proportional with the potential benefit.

Aside from the regulatory agencies and policymakers in the national government, the target users of this guideline on screening strategies include primary care providers, general physicians, specialists, training institutions, payors, patients, the general public, and industry partners.

The burden of disease of the different conditions tackles in the clinical questions are as follows:

1. High climacteric syndrome, which may occur around the time of menopause, is characterized most prominently by the presence of vasomotor symptoms and is associated with metabolic changes in women and decreased quality of life.
2. Hypocalcemia is most commonly caused by renal failure, hypoparathyroidism, and vitamin D deficiency. Treatment requires supplementation with oral calcium with or without vitamin D. Hypercalcemia on the other hand is most commonly caused by hyperparathyroidism. Both hypocalcemia and hypercalcemia, when severe, can lead to cardiovascular (CV) dysfunction, among other symptoms.
3. Prediabetes, an intermediate state of hyperglycemia above normal but below diabetes threshold, is a risk factor for developing diabetes, which is associated with the development of nephropathy, retinopathy, neuropathy, and macrovascular disease.
4. Chronic kidney disease is one of the leading causes of death and disability worldwide. Funding for CKD alone accounts for one of the largest expenses of the Philippine Health Insurance Corporation.
5. Hyperuricemia is a central feature of gout, but not all individuals with hyperuricemia develop gout. Hyperuricemia is also associated with nephrolithiasis and metabolic syndrome.
6. Malnutrition, which refers to imbalances between a person's energy intake and expenditure, is an increasing global health concern. The prevalence of overweight and obesity is increasing in the Philippines while the burden of chronic energy deficiency remains.
7. Anemia is decreasing in prevalence in the Philippines, but the prevalence of non-nutritional anemias, such as thalassemia and other hemoglobinopathies, is increasing. Screening for nutritional anemias may be beneficial since replacement of micronutrient deficiencies will correct the anemia. Thus, it becomes important to differentiate nutritional from non-nutritional anemias.
8. Differences in timing of sexual maturity may have a profound impact on the well-being of a growing adolescent, and screening for these disorders may allow early intervention and support for psychosocial development.

Thus, the need to see the importance of screening in individuals for the particular diseases. This consensus statement looks into the apparently healthy, asymptomatic adult Filipino individuals. This is defined as someone who does not have any symptoms of disease. The consensus panel also defined this individual as devoid of modifiable risk factors such as diabetes, hypertension, and smoking. The critical outcomes include all-cause mortality, CV mortality, renal replacement therapy, and quality of life.

2. Scope and Purpose

Renal, metabolic, nutrition, and endocrine disorders cause significant burden of disease in the adult population. Menopausal symptoms occur in approximately one-third of women 50 years or older, with hot flushes being the most common symptom.[7] Hypocalcemia is present in around one-fourth of elderly patients[8],whereas hypercalcemia is observed in only 0.1% of the population[9]. Prediabetes, a significant risk factor for the development of diabetes, is found in 27.7% of Filipino adults[10]. Chronic kidney disease has a global prevalence of 9.1% and is an important risk for CV disease (CVD) and mortality.[11] Hyperuricemia is seen in 25% of Filipinos[12], being twice as common in men compared to women[13]. Obesity, a significant risk for diabetes and CVD, is increasing in prevalence, and as much as 36.6% of Filipinos are overweight or obese.(10) Anemia, with a prevalence of 7.2% in the Philippines, is more common in women and in the elderly.(10) Delayed puberty occurs in approximately 5% of adolescents[14], whereas precocious puberty occurs in 1 in 5,000 to 10,000 children.[15]

For this CPG, the clinical questions involved the conditions described above: high climacteric syndrome, hypocalcemia and hypercalcemia, prediabetes, chronic kidney disease, hyperuricemia, malnutrition, nutritional anemia, and sexual maturity. All clinical questions will involve asymptomatic or apparently healthy adults, except for high climacteric syndrome, which are involve only women around the age of menopausal transition, and sexual maturity, which involve adolescents. The following general outcomes were considered: all-cause mortality, CV mortality, quality of life, renal replacement therapy, adverse effects due to screening or to treatment, diagnostic accuracy of screening, and cost-effectiveness of the screening tool.

3. CPG Development Methodology

3.1. Organization of the Process

Following the international standards, the DOH (1) outlined the guideline development process into four phases: 1) preparation and prioritization, 2) CPG generation, 3) CPG appraisal, and 4) implementation in the Manual for CPG Development[16].

The Steering Committee (SC) facilitated the whole CPG formulation process. In the preparation and prioritization phase, the SC set the CPG objectives, scope, target audience, and clinical questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included. SC members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries and evidence-based draft recommendations of the evidence review experts (ERE), and voting on final recommendations during the *en banc* consensus panel review. They invited the relevant organization to nominate individuals who can become part of the consensus panel.

The ERE or the technical working group were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the consensus panel members to finalize the recommendations.

The Steering Committee convened the Consensus Panel (CP), considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual[16]. Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policymakers, patient advocates, allied medical practitioners, and physicians from different settings (e.g., public primary care settings, private practice, occupational health settings). The physicians were members of the different medical societies, namely, Association of Municipal Health Officers of the Philippines, Food and Nutrition Research Institute, Philippine Academy of Family Physicians, Philippine Alliance of Patient Organizations, Philippine Association of Nutrition, Philippine College of Endocrinology, Diabetes, and Metabolism, Philippine College of Physicians, and Philippine Society of Nephrology.

The CP was tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, they prioritized critical and important outcomes; discussed necessary considerations revolving around the recommendations and voted on each recommendation and its strength. They participated in a modified Delphi activity to decide on recommendations that were not resolved during the *en banc* meeting.

Each nominee was required to fill out and sign a declaration of interest form and submit their curriculum vitae. The SC and the COI Committee screened the nominees for any possible conflict of interest that may bias their decisions. Those with significant potential

COI based on the decision of the COI Committee were not allowed to vote during the *en banc* meeting but fully participated in the panel discussions.

This guideline was funded jointly by the DOH and the National Institutes of Health.

3.2. Evidence Summaries

The clinical questions were developed using the population, intervention, comparator and outcome (PICO) format. The ERE searched and appraised international practice guidelines related to periodic health screening, including but not limited to those of the Canadian Task Force on Preventive Health Care, U.S. Preventive Services Task Force, National Institute for Health and Care Excellence. If the CPG were of good quality and done within 5 years, the evidence summaries of the CPG were adopted.

For this task force, the initial diseases considered were menopause, prediabetes, osteoporosis, chronic kidney diseases, obesity and nutritional anemia. An initial set of questions were drafted by the steering committee on the selected topics of interest. Upon deliberation of the clinical questions with the central committee, some changes were made. Menopause was considered a physiologic state rather than a disease, thus the steering committee decided to look into women who have high climacteric syndrome as they have a high risk for CVD. It was also decided that instead of focusing on just obesity, the team look at malnutrition as a diseased state. Osteoporosis was given to a different task force, and thus questions on calcium metabolism was added to the recommendations.

During the CPG development, questions on hyperuricemia and sexual maturity were added to the task force. Thus, the eight CQs were addressed: high climacteric syndrome, calcium metabolism, prediabetes, CKD, hyperuricemia, malnutrition, nutritional anemia, and sexual maturity

The results of the appraisal of existing CPGs and their evidence summaries determined the need for a systematic search in electronic databases (MEDLINE via PubMed, Cochrane Central Register of Controlled Trials [CENTRAL], Google Scholar) for the need to do de-novo systematic reviews and meta-analysis (SRMA) for each question. Relevant local databases and websites of medical societies were also utilized in the search. Keywords were based on PICO (MeSH and free text) set for each question. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. Evidence reviewers appraised the directness, methodological validity, results, and applicability of each relevant article included. RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE generated evidence summaries for each of the eight questions. Each evidence summary included evidence on the burden of the problem, and diagnostic performance, benefits, harm, and social and economic

impact of the screening test/intervention. Evidence/information that will facilitate in the decision (i.e. cost of screening test, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The certainty of evidence was assessed using the GRADE approach[17].

Table 1. Basis for Assessing the Certainty of Evidence using GRADE Approach.

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Factors that lower quality of the evidence are:

- Risk of bias
- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

3.3. Formulation of the Recommendations

Draft recommendations were formulated based on the certainty of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps. Prior to the series of online consensus panel meetings, the consensus panel received the draft recommendations together with evidence summaries based on the EtD framework shown in Table 2. These recommendations, together with the evidence summaries, were presented during the *en banc* meeting.

Table 2. Detailed Considerations Based on the EtD Framework.[1]

1. Is the problem a priority?
2. How accurate is the test?
3. How substantial are the desirable anticipated effects?
4. How substantial are the undesirable anticipated effects?
5. What is the certainty of the evidence of test accuracy?
6. Is there important uncertainty about or variability in how much people value the main outcomes, including adverse effects and burden of the test and downstream outcomes of clinical management guided by the test results?

7. Does the balance between desirable and undesirable effects favor the test or the comparison?
8. How large are the resource requirements (costs)?
9. What is the certainty of the evidence of resource requirements (costs)?
10. Does the cost-effectiveness of the test favor the test or the comparison?
11. What would be the impact on health equity?
12. Is the test acceptable to key stakeholders?
13. Is the test feasible to implement?

The strength of each recommendation (i.e. strong or weak) was determined by the panel considering all the factors mentioned above. Strong recommendation means that the panel is "confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects" while weak recommendation means that the "desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident"[18].

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed.[17] If consensus was not reached in the first voting, questions, and discussions were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based draft recommendations were also revised based on input arrived at by consensus in the *en banc* discussions.

3.4. Planning for Dissemination and Implementation

All recommendations and evidence summaries will be posted in a web-based and mobile app. The SC discussed with relevant stakeholders such as DOH and PHIC to prepare a dissemination plan that will actively promote the adoption of this guideline with strategies for copyrights. Suggestions ranged from making guidelines available on websites, press conferences, social media sites, professional society conventions, and journal publications.

3.5. External Review

The CPG was reviewed by three independent stakeholders, who were not members of the Task Force. The reviewers provided their insights on the content, clarity, acceptability, applicability, and feasibility of the recommendations. Comments from the reviewers were considered in writing the final CPG.

4. Recommendation and Evidence Summaries

4.1. Serum Follicle-stimulating Hormone, Luteinizing Hormone, and Estradiol in Screening for High Climacteric Syndrome

RECOMMENDATIONS

1. **Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest against routine screening for high climacteric syndrome using follicle stimulating hormone (FSH).**
   (weak recommendation, low certainty evidence)

2. **Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest against routine screening for high climacteric syndrome using luteinizing hormone (LH).**
   (weak recommendation, low certainty evidence)

3. **Among apparently healthy, asymptomatic Filipino women aged 45–55 years, we suggest against routine screening for high climacteric syndrome using estradiol**
   (weak recommendation, low certainty evidence)

Justification and Considerations
High climacteric syndrome is diagnosed clinically. There were no studies which looked at the use of serum FSH, LH, and estradiol in screening for high climacteric syndrome. Routine use of hormonal tests for high climacteric syndrome does not significantly alter the management. Treatment of high climacteric syndrome is inconclusive when it comes to overall and CV mortality. With low certainty of evidence, treatment is associated with increased coronary heart disease and stroke.

4.1.1. Burden of disease

Disease Frequency
Among Filipino women, the average menopausal age is 48-51 years of age.[19, 20] Onset of menopausal syndrome marks the main clinical effect of estrogen decline.[21] It includes hot flushes, night sweats, urogenital atrophy, sexual dysfunction, mood changes, bone loss and metabolic changes predisposing women to CVD and diabetes. The age at menopause is used to mark the timing of menopause and is confirmed after a year of amenorrhea.[22] Menopause-related symptoms occur in the majority of women (50–85%) 45 years old and above and are associated with socioeconomic cost and significantly reduced quality of life from increased anxiety and stress arising from sleep deprivation, mood swings, and unpredictable hot flushes.[7, 23]

Severity of Disease

The menstrual transition which often begins between ages 45 and 55 years is a period of significant changes in cardiometabolic factors (lipids, vascular health, metabolic syndrome, visceral adiposity). Vasomotor symptoms in particular, reported at midlife have been linked to adverse lipid profile, insulin resistance and greater risk of hypertension. Healthcare providers may consider an early prevention-based approach for women at this stage to decrease future CV events.[24]

Climacteric is defined as the phase in the aging of women marking the transition from the reproductive to the nonreproductive state. It incorporates the perimenopause by extending for a longer variable period before and after the perimenopause. Climacteric syndrome occurs when climacteric is associated with a constellation of symptoms. Many cohort and cross-sectional studies were performed to characterize climacteric symptoms. The most consistently found were vasomotor symptoms such as hot flashes and diaphoresis; and vaginal dryness. Other less common symptoms include: sleep disturbances, mood changes, urinary tract symptoms and sexual problems including loss of libido and dyspareunia.[25]

Natural History of the Disease

On average, frequent or moderate to severe vasomotor symptoms (VMS) of menopause last for 7–10 years. Women with VMS can typically be classified into four groups. In the early onset group, women had VMS early in the menopausal transition, before the cessation of menses, and their VMS declined with their final menstrual period. Women in the later onset group had their VMS largely after their menses have ceased, and VMS continued into their post-menopausal years. In the mild VMS group, women had few or no VMS over the transition. Lastly, in the fourth group, women started their VMS before their menses have stopped, and continued well into postmenopause. In the United States (US), Asian women experienced VMS less compared to White and African American counterparts.[26]

Management of the Disease

Management of high climacteric syndrome requires identification of CV risk and breast cancer risk. For women without contraindications, hormone therapy options include estrogen plus progestogen, estrogen plus bazedoxifene, and tibolone for women with uterus, and estrogen alone for women without uterus. Nonhormonal prescription therapies include gabapentin, prebalin, venlafaxine, and clonidine.[27]

Economic Impact of the Disease

In a retrospective study done in the US[28], the annual direct cost of menopausal symptoms was US$248 per patient in 2010–2012 dollars. Comparing the cost with other diseases, it was found that treatment for menopausal symptoms had higher annual cost that the cost of treatment for osteoporosis or dyslipidemia. A survey[29] done among 509 women in the United Kingdom (UK) who were 50 years and older showed that around one-third of the participants reported moderate to severe difficulties at work due to menopausal symptoms.

Social Impact of the Disease

The menopausal transition is associated with decreased quality of life. Specifically, vasomotor symptoms, weight gain, and fatigue had significant direct effects on symptoms of anxiety, depression, and psychological distress.[30] Compared with work-related activities, daily activities were more significantly affected by high climacteric syndrome among women. These activities include working around the house, shopping, taking care of children, exercising, and studying.[31]

4.1.2. Benefits and Harms of Screening Tests

There were no direct studies found on screening using symptoms and hormonal tests such as LH, FSH and estradiol for climacteric syndrome versus no screening among apparently, healthy asymptomatic women. Instead, 5 indirect studies were found to be indirect evidence, 4 cross sectional studies on the reliability of hormonal tests (FSH, LH, estradiol) and 1 randomized-controlled study on the treatment of menopause. The characteristics of included studies are included in Appendix 10.1.

All-cause Mortality, Cardiovascular Mortality, Coronary Heart Disease, and Stroke

The largest randomized controlled trial (RCT)[32] evaluated the effects of hormonal therapy (HT) in postmenopausal women. The Women's Health Initiative (WHI) included 27,347 postmenopausal women aged 50–79 years recruited from 1993 to 1998 at 40 US clinical centers. The 16,608 women with intact uterus were randomized to estrogen plus progesterone or placebo. The remaining 10,739 women with prior hysterectomy received either estrogen alone or placebo. The median follow up for estrogen plus progesterone and estrogen alone were 8.2 years and 6.6 years, respectively. It was designed to determine benefits and risks of HT when taken for chronic disease prevention by predominantly healthy postmenopausal women. Primary outcomes were coronary heart disease and invasive breast cancer. Other global indices such as stroke, pulmonary embolism, colorectal cancer, endometrial cancer, hip fracture and death were also investigated.(32,33) WHI showed inconclusive results for overall and CV mortality but a trend toward harm for having coronary heart disease and stroke with low certainty of evidence due to its indirectness (table 3).[32, 33]

Table 3. Randomized controlled trial[32] evaluating the use of conjugated equine estrogen plus medroxyprogesterone acetate on critical outcomes.

Outcomes	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
All-cause mortality	HR 0.99	0.99, 1.08	Inconclusive	Low
Cardiovascular mortality	HR 0.97	0.82, 1.14	Inconclusive	Low
Coronary heart disease	HR 1.04	0.89, 1.23	Harm	Low
Stroke	HR 1.16	1.00, 1.35	Harm	Low

CI, confidence interval; *HR*, hazards ratio.

4.1.3. Diagnostic Performance of Screening Tests

All of the four cross-sectional studies explored the reliability of FSH as a diagnostic test for menopause. Only one study[34] included LH and estradiol. These studies included data from premenopausal and postmenopausal women and compared the ability of hormonal tests to discriminate between pre- and post-menopausal status.[34–37] The results of these studies are summarized in table 4.

Table 4. Reliability and Concordance of Serum Follicle-stimulating Hormone, Luteinizing Hormone, and Estradiol in the Diagnosis of Menopause.

Test result	Number of results per 1,000 Patients Tested (95% CI) Prevalence 26%	Number of Studies	Certainty of Evidence (GRADE)
Follicle-stimulating Hormone			
True positives	191 to 258	4	Very low
False negatives	2 to 69		
True negatives	522 to 718		Very low
False positives	22 to 218		
Luteinizing Hormone			
True positives	255 (0 to 0)	1	Very low
False negatives	5 (260 to 260)		
True negatives	718 (0 to 0)		Very low
False positives	22 (740 to 740)		
Estradiol			
True positives	218 (0 to 0)	1	Very low
False negatives	42 (260 to 260)		
True negatives	718 (0 to 0)		Very low
False positives	22 (740 to 740)		

CI, confidence interval.

A cross-sectional study[34] done in 111 healthy, ovulatory and postmenopausal Korean women with no endocrine disorders and no evidence of polycystic ovarian syndrome investigated age-dependent and postmenopausal changes in the serum levels of anti-Mullerian hormone (AMH), inhibin B, insulin-like growth factor-I (IGF-I), insulin-like growth factor binding protein 3 (IGFBP-3), FSH, LH, and estradiol in 144 women aged 20-59 years old. Area under the receiver operating characteristic curve (ROC AUC) analyses were performed to assess the ability of each marker to discriminate between the pre- and postmenopausal status. This study showed that the sensitivity and specificity of FSH to diagnose menopause were 99.1% and 97%, respectively. LH had sensitivity and specifity of 98.2% and 97%, respectively; and estradiol had sensitivity and specificity of 83.8% and 97%, respectively.[34] Another cross-sectional study had similar results. In this cross-sectional study which investigated the sensitivity of vaginal pH and serum FSH level in diagnosing menopause in 120 women in India who had their last menstrual period more than a year prior to the study, the sensitivity of serum FSH level to diagnose menopause was 85%.[35]

The third cross-sectional study assessed the reliability using store sera from 60 women enrolled in the New York University Women's Health Study. The study showed that the reliability of a single log-transformed FSH measurement, as determined by the intraclass correlation coefficient (ICC), was 0.09 for premenopausal women (95% confidence interval [CI] [0, 0.54]) and 0.70 for postmenopausal women (95% CI [0.55, 0.82]), suggesting that a single measurement is sufficient to characterize the serum FSH level in postmenopausal women. However in premenopausal women, the reliability coefficient was low, suggesting that a single determination is insufficient to reliably estimate a woman's true average serum FSH level. Thus, repeated measurements must be done in premenopausal women.[36]

Lastly, a study using data from National Health and Nutrition Examination Survey (NHANES) 1999–2000 showed that levels of FSH and LH increase significantly with reproductive stage (geometric mean FSH levels for successive stages: reproductive, 7.0 mIU/mL; menopause transition, 21.9 mIU/mL; and postmenopause, 45.7 mIU/m). FSH cutoff points between the reproductive and menopause transition stages (FSH 13 mIU/mL) and between the menopause transition and postmenopause stages (FSH 45 mIU/mL) were neither sensitive nor specific. They concluded that FSH by itself has limited utility in distinguishing between different reproductive stages.[37]

All four concordance studies had a very low level of certainty because the population were not specifically high risk climacteric patients, cut off values were not prespecified and there was an unclear reference standard, they are only reliability/concordance studies and for FSH, the 4 studies used different cut off values with varying sensitivities and specificities.

4.1.4. Cost Implication

There are no available studies on the cost-effectiveness of screening for high risk climacteric syndrome versus no screening in healthy, asymptomatic women. Cost of work up for menopause and hormone replacement therapy using available data in the country are presented in table 5.

Table 5. Costing Data in Screening for High Climacteric Syndrome.

	Cost in ₱
Symptom Check	
Consultation	500–1,000 per visit
Hormone Level Testing	
Luteinizing hormone	900–1,400
Follicle-stimulating hormone	900–1,000
Estradiol	900–3,000
Hormone Replacement Therapy	
Estrogen	
Conjugated equine estradiol (CEE)	40–80/tab
Oral estradiol	20–100/tab
Transdermal patch	2,000
Topical gel	800
Vaginal Tab	125
Vaginal cream	900
Progestin	
Micronized Progesterone	50–70/tab
Dihydrogesterone	89.50/tab
Medroxyprogesterone Acetate (MPA)	89/tab, 120–136/vial
Norethisterone Acetate	50/tab
Estrogen-Progesterone	25–35/tab

The value screening of menopausal women with expensive hormone tests including progesterone, luteinizing hormone, dehydroepiandrostenedione levels, predictable high FSH, low estrogen and testosterone levels remains controversial and contributes to unnecessary cost. On the other hand, testing for lipid profile, random blood sugar, complete blood count (CBC) or thyroid function test is appropriate for women with relevant risk factors, signs and symptoms which may change management taking into consideration the cost of each test. However, it should be noted that there is no need to

do a battery of tests as part of the work up of a normal postmenopausal before she can be offered or started hormone replacement therapy.[38]

The Philippine Health Insurance Corporation (PHIC) does not cover menopause and its management. Health cards as well do not cover hormone therapy services. Senior citizens can avail of the 20% discount on medications and services.

A cost-effectiveness model was developed to evaluate outcomes associated with hormone therapy in younger and older postmenopausal women 50–65 years old. Primary outcomes included quality-adjusted life-years (QALYs) and incremental cost per QALY gained. In this model, hormone therapy for 5–30 years in younger postmenopausal women increases QALY and is cost effective (a gain of 1.49 QALYs with an incremental cost of $2,438 per QALY gained, compared with no treatment). However, hormone therapy in later years results in a loss of QALY for several years before a net gain can be achieved (a net gain of 0.11 QALYs with a cost of $27,953 per QALY gained with a loss of QALYs in the first 9 years).[39]

4.1.5. Equity, Acceptability, and Feasibility

Ethical

A local study suggests that climacteric symptoms were highly prevalent among Filipino women. Majority have accepted menopause-related disorders as part of a woman's life cycle and that climacteric symptoms are bearable and not life-threatening; and therefore not a priority for a consult. For women who can afford hormonal replacement therapy (HRT), fear of cancer was the highest hindrance to HRT.[19]

A study conducted among gynecologic oncology patients at the Philippine General Hospital concluded that the majority of them were not aware of the symptoms of menopause and its treatment. Sixty four percent (4%) of the respondents believed that menopause requires no treatment. Most of them (92%) have not availed of any treatment for menopause mainly because of cancer treatment and family expenses.[40]

Social

A cross-sectional study done among Filipino women aged 40 years and above at a tertiary hospital concluded that there is no significant association between sociodemographic factors such as BMI, marital status, intake of oral contraceptive pills and climacteric symptoms as well as with the timing of menopause.[20] Another cross-sectional study[3] concluded that the knowledge on menopause has not increased significantly after almost 2 decades compared with previous studies. Majority of the women in the study had fair knowledge on menopause but more than half of them have no knowledge on hormone replacement therapy. They were not familiar with the benefits of HRT but noted that there’s a high percentage of women (78%) who will take HRT if advised by their doctors.[3] The study served as a guide to the clinicians as to how patients perceived menopause and HRT; and the importance of health education in every patient encounter.

Health Systems

In 1991, the Philippine General Hospital Menopause clinic was established which included a multidisciplinary team of gynecologists, cardiologists, psychiatrists, orthopedic surgeons, internists, nutritionists and physical therapists. It spearheaded several research on menopause and provided training for obstetrics and gynecology residents who want to establish menopause clinics. The Philippine Society of Climacteric Medicine requires all accredited training centers of the Philippine Obstetrical and Gynecological Society (POGS) to establish a menopause clinic. Presently, there are 91 POGS accredited residency training hospitals in the country.

4.1.6. Recommendations from Other Groups

The North American Menopause Society[41, 42], the National Institute for Health and Care Excellence (NICE)[43], the Indian Menopause Society[44], and the Endocrine Society[27] made similar recommendations in that routine hormonal testing is not recommended in the diagnosis of menopause. Their specific recommendations are summarized in table 6.

Table 6. Recommendations from Other Groups on the Use of Laboratory Markers in the Diagnosis of Menopause.

Group or Agency	Recommendation
North American Menopause Society (2014)[41]	Recommends a thorough history and focused physical exam to guide clinicians in managing the symptoms of menopause transition (Level II). Hormone measurements to determine menopause status are not routinely indicated.
National Institute for Health and Care Excellence (NICE) (published 2015, updated 2022)[43]	Recommends an individualized approach in the diagnosis, investigation and management of perimenopause and menopause. Does not recommend the use of laboratory (anti-mullerian hormone, inhibin A/B, estradiol, antral follicle count, ovarian volume) and imaging tests to diagnose perimenopause or menopause in women aged over 45 years.
Indian Menopause Society (2013)[44]	Menopause is diagnosed retrospectively by history. Laboratory markers such as FSH and anti-mullerian hormone are preferably restricted for use in special situations and for fertility issues.
Endocrine Society (2015)[27]	Recommends diagnosing menopause based on the clinical criteria of the menstrual cycle. Among patients who underwent hysterectomy without bilateral oophorectomy, they suggest to base it on the presence of vasomotor symptoms, if establishing the diagnosis of menopause is necessary for patient management and to determine FSH and serum estradiol levels when indicated.

4.2. Serum Calcium, Electrocardiogram, and Bone Mineral Density in Screening for Hypocalcemia or Hypercalcemia

RECOMMENDATIONS

1. **Among apparently healthy, asymptomatic adults, we recommend against routine screening for hypocalcemia or hypercalcemia using serum calcium.**
   (strong recommendation, low certainty evidence)

2. **Among apparently healthy, asymptomatic adults, we recommend against routine screening for hypocalcemia or hypercalcemia using electrocardiogram (ECG).**
   (strong recommendation, low certainty evidence)

3. **Among apparently healthy, asymptomatic adults, we recommend against routine screening for hypocalcemia or hypercalcemia using bone mineral density (BMD).**
   (strong recommendation, low certainty evidence)

Justification and Considerations
There were no studies that involved the use of serum calcium as a routine screening test for asymptomatic adults. Likewise, no studies were found using electrocardiogram or bone mineral density testing in screening for hypocalcemia or hypercalcemia. The panel made a strong recommendation against the use of serum calcium, electrocardiogram, and bone mineral density in screening for hypocalcemia or hypercalcemia due to absence of evidence.

4.2.1. Burden of disease

Calcium, the most abundant extracellular cation in the human body, is essential for many metabolic processes including coagulation, neuromuscular signaling, cardiac contractility and hormone secretion. Calcium metabolism mainly depends on a series of feedback mechanisms involving the parathyroid hormone (PTH), calcitonin and vitamin D.[8] Disorders of calcium homeostasis may have an impact on systemic function and often indicate presence of an underlying disease. In the clinical setting, elevation (hypercalcemia) or reduction (hypocalcemia) may be associated with life-threatening consequences.

Disease Frequency

The prevalence of hypercalcemia in the emergency department is 0.6% and its overall prevalence is 1/1000 in the general population.[8] It is most commonly caused by primary hyperparathyroidism and malignancy, which accounts for 90% of the cases. In the Philippines, primary hyperparathyroidism is more commonly detected when patients manifest skeletal abnormalities, renal calculi, and musculoskeletal symptoms.[45] In

malignancies complicated by hypercalcemia, the underlying disease is often clinically evident upon presentation.

On the other hand, there is paucity of data on the prevalence of hypocalcemia in the general population, but it is commonly observed in institutionalized patients. A cross-sectional study in a tertiary care in Nepal determined the prevalence of hypocalcemia in the elderly was at 24.1%.[9] Hypoparathyroidism, vitamin D deficiency and post thyroidectomy are among its chronic etiologies, but in general, renal failure remains the most common cause in adults. Acute hypocalcemia may be caused by sepsis, acute kidney injury, significant blood transfusion, and burns.

In the hospital setting, a retrospective study[46] in 2018 identified incidence of hypocalcemia at 27.72% (n = 3,420) and hypercalcemia at 4.74% (n = 585) in the study population. The highest prevalence of hypocalcemia was found in patients over 65 years (n = 2,097, 61.31%), while the highest prevalence of hypercalcemia was observed in the younger age group 0–18 years.[46] To date, there is no local literature on the prevalence of hypercalcemia and hypocalcemia among Filipinos.

Natural Course of the Disease

Patients with mild elevation or reduction in serum calcium levels may be asymptomatic and initially tolerated. With increased serum calcium at 12–14 mg/dL (3–3.5 mmol/L), patients may present with symptoms of nausea, muscle weakness, dehydration, and changes in sensorium. Severe hypercalcemia, defined as calcium >14 mg/dL (3.5 mmol/L), have progression of these symptoms and are often life-threatening.[47] A systematic review done in 2016[48] showed higher calcium concentrations were associated with greater risk of heart failure (hazards ratio [HR] for the fifth versus the first quintile, 1.48; 95% CI [1.29, 1.70]). The risk for CV events is increased by 8% for each standard deviation increase in baseline serum calcium. The same study(48) also noted statistically significant associations between increased serum calcium at baseline and mortality. For disease-related hypercalcemia, a meta-analysis done in 2021[49] on risk of fractures in patients with primary hyperparathyroidism showed an increased risk of any fracture compared to control (odds ratio [OR] 2.01, 95% CI [1.61, 2.50]).

As with hypercalcemia, patients with hypocalcemia may present with mild symptoms to life-threatening conditions. Acute manifestations may include neuromuscular irritability, seizures, papilledema, psychiatric disturbance, and cardiac dysfunction. Hypocalcemia may also present with symptoms specific to its underlying disease. Cataracts, dental abnormalities, and basal ganglia calcification are common among patients with hypoparathyroidism. Hypocalcemia secondary to vitamin D deficiency may lead to osteomalacia in adults.[50]

Management of the Disease

Management of hypercalcemia and hypocalcemia are usually initiated in the hospital setting. Hypercalcemia may be managed with intravenous hydration, use of bisphosphonates and corticosteroids. However, the definitive management primarily depends on the underlying cause. On the other hand, management of hypocalcemia

depends on severity and accompanying complications. Acute symptomatic hypocalcemia is managed with intravenous calcium gluconate. Chronic hypocalcemia is treated based on its etiology, but often involves calcium and vitamin D supplementation.[50]

4.2.2. Benefits and Harms of Screening Tests

There are no direct studies on the benefits and harm of screening for hypercalcemia and hypocalcemia among healthy asymptomatic adults. Indirect evidence on early treatment of hypercalcemia-related diseases such as hyperparathyroidism may lead to favorable outcomes.

Early Treatment of Hyperparathyroidism

A 2020 SRMA[51] of four RCTs compared efficacy of parathyroidectomy over conservative management in patients with mild asymptomatic hyperparathyroidism on skeletal outcomes, risk of nephrolithiasis and quality of life. There was no difference in fracture risk between parathyroidectomy and active surveillance (total fracture pooled analysis relative risk [RR] 0.31, 95% CI [0.11, 1.10]). With regards to bone mineral density (BMD) changes, higher BMD values were observed in the parathyroidectomy group for the lumbar spine (mean difference 3.55, 95% CI [1.81, 5.29]) and total hip (mean difference 3.44, 95% CI [1.39, 5.49]), but no difference in femoral neck and arm. On risk of nephrolithiasis, no difference was observed between the two groups. Likewise, no difference was observed for quality of life indices, except for general health.[51]

For medical management, an RCT[52] done in 2004 compared alendronate to placebo on patients with primary hyperparathyroidism for outcomes of fractures and BMD (RCT, n = 44). Treatment with alendronate showed significant increase in lumbar spine BMD from baseline after 24 months (.85%, micro(d) 0.052, ± 0.94% se, p <0.001). In addition, alendronate showed significant reduction in bone turnover markers. No fracture was observed between the two groups.[52]

A 10-year prospective randomized controlled trial[53] on mortality and morbidity of patients with mild primary hyperparathyroidism evaluated outcomes following parathyroidectomy compared to observation. After 15 years of extended follow up, no significant difference in mortality rate between the surgery and observation group (HR 1.23, 95% CI [0.68, 2.23], p = 0.68). There was also no significant difference in time to first event between the 2 groups in outcomes of CV events (HR 0.81, 95% CI [0.33, 1.99], p >0.05), peripheral fractures (HR 0.75, 95% CI [0.37, 1.50], p >0.05), cerebrovascular disease (HR 0.73, 95% CI [0.20, 2.65], p >0.05), cancer (HR 1.78, 95% CI [0.71, 4.48], p >0.05) and nephrolithiasis (HR 0.34, 95% CI [0.06, 1.82], p >0.05).[53]

4.2.3. Diagnostic Performance of Screening Tests

Serum calcium

There are no controlled trials on the use of serum calcium among healthy asymptomatic adults. Several studies have compared serum calcium to ionized calcium (iCa) among special groups and diseases. A retrospective analysis done in 2016[54] evaluated the validity of unadjusted serum calcium and serum calcium adjusted for albumin (Payne formula) among hospitalized adult patients using iCa as reference standard. The

intraclass correlation coefficients (ICC), Pearson's correlation for the z scores and level of agreement of unadjusted total calcium (ICC 0.76, R 0.86, k 0.48) were higher than Payne formula (ICC 0.73, R 0.82, k 0.18). Better relationship was seen between iCa and unadjusted serum calcium for those with albumin more than 30 g/L (ICC 0.81, R 0.87). In addition, both unadjusted calcium and Payne formula have high specificity for hypercalcemia [95.4% (95% CI, 93.4 to 97.0%) vs. 75.5% (95% CI, 71.8 to 79.%) respectively] and hypocalcemia [91.6% (95% CI, 88.0% to 94.3%) vs. 99.4% (95% CI, 97.8 to 99.9%)] but fairly low sensitivity. However, the study has serious risk of bias and indirectness, hence deemed very low certainty of evidence.[54]

Electrocardiogram

Observational studies showed QT interval duration was inversely associated with total serum and ionized calcium.[55] However, there are no direct clinical studies on the use of electrocardiogram (ECG) for screening or diagnosing hypercalcemia or hypocalcemia. A study[56] on 24-hour ECG as screening for primary hyperparathyroidism was conducted with the premise that patients with hyperparathyroidism have increased calcium plasma concentration. Though significant higher calcium concentration was found compared to controls (2.38 ± 0.12 vs. 2.92 ± 0.29 mmol/l; p <0.001), there were no significant differences in average QT interval between the two groups. Despite being a correlational study rather than a diagnostic study, the authors concluded that 24-hour outpatient ECG is not suitable for primary hyperparathyroidism screening.[56]

Bone mineral density

There are no studies on the use of bone mineral density for screening for hypocalcemia or hypercalcemia.

4.2.4. Cost Implication

There are no studies on the cost effectiveness of screening for hypercalcemia or hypocalcemia among healthy asymptomatic adults. Locally, the cost for serum calcium test ranges from ₱200 to ₱400, and around ₱1000 for ionized calcium depending on the institution. Electrocardiogram costs ₱100–450. Bone mineral density test, on the other hand, ranges from ₱5,000 to ₱10,000. These tests are often ordered by physicians upon assessment of patients presenting with symptoms or those at risk to develop calcium-related disorders.

4.2.5. Equity, Acceptability, and Feasibility

A case-control study[57] done in 2014 among 381 primary care patients in Sweden evaluated quality of life and health care consumption between patients with elevated or normal serum calcium. Patients with increased serum calcium have significantly lower scores in all domains of the 36-item Short Form Health Survey questionnaire. These domains of health status include physical functioning, physical role functioning, bodily pain, general health, vitality, social role functioning, emotional role functioning and mental health. Patients with elevated serum calcium had significantly more sick leave and drug treatment than normocalcemic patients. In addition, hypercalcemic patients were also noted to have more hospital days and care occasions but these were not significant.[57]

There are no studies on values, patient preference and acceptability of hypercalcemia and hypocalcemia screening among healthy adults.

4.2.6. Recommendations from Other Groups

Currently, there are no clinical guidelines on routine screening for hypercalcemia and hypocalcemia among healthy, asymptomatic adults. Guidelines for screening and management of hypercalcemia are specific for hypercalcemia from malignancy or hyperparathyroidism.

4.3. Fasting Plasma Glucose and Hemoglobin A_{1C} in Screening for Prediabetes and Type 2 Diabetes Mellitus

RECOMMENDATIONS

1. **Among apparently healthy adults aged 40 years above, or younger if with risk factors, we recommend screening for prediabetes and type 2 diabetes mellitus using fasting plasma glucose (FPG).**
   (strong recommendation, moderate certainty evidence)

2. **Among apparently healthy adults aged 40 years above or, younger if with risk factors, we suggest screening for prediabetes and type 2 diabetes mellitus using hemoglobin A_{1C} (HbA_{1C}).**
   (weak recommendation, moderate certainty evidence)

Justification and Considerations

There were no direct studies comparing screening versus no screening for prediabetes. The consensus panel initially gave a conditional recommendation but the consensus panel reviewed the evidence and voted for weak recommendation. Several randomized controlled trials with low to moderate certainty of evidence favors screening for prediabetes in preventing progression to T2DM, but not in reducing mortality, CV events, or microvascular complications. Hemoglobin A_{1C} (HbA_{1C}) should only be done in laboratories certified by the National Glycohemoglobin Standardization Program. The use of the 2-hour 75 g oral glucose tolerance test (OGTT) may be useful in individuals with high CV risk or prior diagnosis of prediabetes, but is cumbersome and is not appropriate for apparently healthy adults without risk factors. Targeted screening for prediabetes and T2DM for people with risk factors is cost-effective.

4.3.1. Burden of disease

Prediabetes is an intermediate state of hyperglycemia with glycemic parameters above normal but below the diabetes threshold.[58] Increasing evidence has been linked already to prediabetes as a major risk factor for the early development of nephropathy, neuropathy, retinopathy and macrovascular disease.[59–61]

Disease Frequency

The International Diabetes Federation in 2017 has estimated that the global prevalence of prediabetes is expected to rise from 7.3% equivalent to 352.1 million people in that year to 8.3% equivalent to 587 million people in the year 2045.[62] In Asia, the incidence of diabetes is increasing, driven by aging, urbanization, and associated lifestyle changes, similar to a sharp increase in obesity, largely caused by economic development, nutrition transition, and increasingly sedentary lifestyles.[63, 64] In the Philippines, the Expanded National Nutrition Survey of the Food and Nutrition Research Council in 2019 has shown that the prevalence of impaired fasting glucose defined as a fasting glucose level of 100 to 125mg/dL has doubled from 13.5 last 2013 to 27.7 in 2019.[10]

Natural History of the Disease

Prediabetes progresses to T2DM in 31% of persons with impaired fasting glucose after 12 years of follow-up and in 41% of persons with prediabetes defined by an HbA_{1C} levels of 5.7–6.4% after 10 years of follow-up. Having both impaired fasting glucose and HbA_{1C} levels of 5.7–6.4% increases risk of developing diabetes (RR 6.90). Higher levels of HbA1C (6.0–6.4%) increases the risk tenfold. People aged above 60 years who have prediabetes appear to progress to diabetes less compared to middle-aged counterparts.[65]

Management of the Disease

Prediabetes can be addressed by both pharmacologic and non-pharmacologic interventions. Lifestyle changes which include diet, nutrition and physical activity as well as specific medications such as metformin, alpha glucosidase inhibitors and thiazolidinediones have been shown delay the progression of prediabetes to overt diabetes.[65]

4.3.2. Benefits and Harms of Screening Tests

No direct studies investigated the effect of screening for prediabetes on all-cause mortality, CV mortality and microvascular complications. Most of available studies investigated interventions on prediabetes and their effect on all-cause mortality and CV events.

A meta-analysis of 38 RCTs[66] assessed behavioral and pharmacologic interventions for prediabetes (table 7). This meta-analysis looked into lifestyle interventions vs. control and specific pharmacologic interventions vs. placebo and association with the outcomes on all-cause mortality and CV events, microvascular complication specifically nephropathy and delaying progression to T2DM. The certainty of evidence on the retrieved data on nonpharmacologic interventions vs placebo were deemed low because of unclear randomization and allocation concealment methods as well as indirectness. Studies on pharmacologic interventions on delaying progression to T2DM were limited by imprecision, inconsistency, and risk of bias and issues indirectness hence certainty of evidence were deemed very low to low.[66]

Table 7. Meta-Analysis[66] Evaluating the Lifestyle and Pharmacologic Interventions for Prediabetes on Critical Outcomes.

Critical Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Lifestyle Interventions vs Control					
All-cause mortality and cardiovascular events	1 meta-analysis of 16 RCTs	Cannot fully estimate			Very low
		1 RCT[67]: RR 0.71[a]	0.51, 0.99	Favors intervention	
		1 RCT[68]: RR 0.57[a]	0.21, 1.58	Inconclusive	
Delaying progression to T2DM	1 meta-analysis of 23 RCTs	RR 0.78	0.69, 0.88	Favors intervention	Moderate
Pharmacologic Interventions vs Control					
Delaying progression to T2DM (metformin)	1 meta-analysis of 3 RCTs	RR 0.73	0.64, 0.83	Favors intervention	Moderate
Delaying progression to T2DM (acarbose)	1 meta-analysis of 3 RCTs	RR 0.64	0.43, 0.96	Favors intervention	Low

Delaying progression to T2DM (thiazolidinedione)	1 meta-analysis of 3 RCTs	RR 0.50	0.28, 0.92	Favors intervention	Low
Nephropathy (valsartan)	1 RCT	HR 0.96	0.28, 3.31	Inconclusive	Low

[a], effect size for all-cause mortality
CI, confidence interval; *RCT*, randomized controlled trial; *RR*, relative risk.

All-Cause Mortality and Cardiovascular Events

Most of the RCTs on lifestyle intervention (diet and nutrition with or without physical activity) in the meta-analysis[66] had follow-up duration of 6 years or less, which were assessed to be provide insufficient evidence to assess effects on mortality, CV events, and other health outcomes (see table 7). Most trials reporting mortality or CVD events had few events with no significant difference between groups. Two trials, however, reported outcomes beyond 6 years. The China Da Qing Diabetes Prevention Study[67] found lower all-cause mortality (28.1% vs. 38.4%, HR 0.71, 95% CI [0.51, 0.99]) and CV mortality (11.9% vs. 19.6%, HR 0.59, 95% CI [0.36, 0.96]) for a six-year combined lifestyle intervention group compared to controls at 23 years of follow-up, favoring intervention. The second trial, the Finnish Diabetes Prevention Study[68], however, found no statistically significant difference for all-cause mortality (2.2 vs. 3.8 deaths per 1000 person-years, HR 0.57, 95% CI [0.21, 1.58]) or composite CV events (22.9 vs. 22.0 events per 1000 person-years, HR 1.04, 95% CI [0.72, 1.51]) over 10 years of follow-up.[66]

Delaying Progression to Type 2 Diabetes

In the meta-analysis[66], 23 RCTs (n = 12,915 participants) assessed the effect of lifestyle interventions in delaying progression of prediabetes to T2DM. Lifestyle interventions decreased the incidence of diabetes by 22% (pooled RR 0.78, 95% CI [0.69, 0.88]). Pharmacologic interventions, namely metformin, α-glucosidase inhibitors, and thiazolidinediones, were all significantly associated with a reduction in progression to diabetes with pooled RRs of 0.73, 0.63, and 0.50, respectively (see table 7).

Microvascular Complications

Only one RCT[69] evaluated the effect of valsartan on microvascular complications in patients with impaired glucose tolerance, specifically end-stage renal disease. There was no significant difference between intervention and control (HR 0.96, 95% CI [0.28, 3.31]).

Safety Outcomes

The following adverse effects of interventions were reported in the meta-analysis: hypoglycemia, gastrointestinal upset, and musculoskeletal events. In four of the trials which reported any hypoglycemia, no statistical difference was found between the pharmacotherapy group and placebo over 8 weeks to 5 years of follow-up. Three trials reported gastrointestinal upset in persons who took metformin. The DPP study reported higher GI symptoms in patients on metformin vs lifestyle intervention (77.8% vs. 30.7%, p <0.017). Lastly, musculoskeletal events such as sprains, strains, and muscle and joint aches, are potential harms of lifestyle intervention, with inconsistent results among the threes RCTs that reported this outcome. In the DPP study, higher rates of musculoskeletal symptoms per 100 person-years in the lifestyle intervention group were reported than in the control group (24.1 vs. 21.1 events per 100 person-years, p <0.017).[66]

4.3.3. Diagnostic Performance of Screening Tests

One SRMA[70] of screening tests specifically on FPG and HbA1C was retrieved. There were no studies retrieved looking into the diagnostic accuracy of history and physical examination as a tool in the screening of prediabetes.

The meta-analysis done in 2016[70] looking into the diagnostic accuracy of screening tests with OGTT as reference standard for prediabetes showed that the pooled sensitivity of HbA1C is 49% (95% CI [0.40, 0.58) and specificity of 79% (95% CI [0.73, 0.84]). FPG had a mean sensitivity of 25% (95% CI [0.19, 0.32]) and specificity of 94% (95% CI [0.92, 0.96]). The study concluded that HbA1C is neither sensitive nor specific for detecting prediabetes; fasting glucose is specific but not sensitive.[70]

Table 8. Diagnostic Performance of FPG and HbA_{1C} for Prediabetes.[70]

Pooled Analysis	Basis	Pooled Estimate	95% CI	Certainty of Evidence
HbA_{1C}				
Sensitivity	1 meta-analysis of 23 cross-sectional studies	49%	0.40, 0.58	Low
Specificity	1 meta-analysis of 23 cross-sectional studies	79%	0.73, 0.84	Low
FPG				
Sensitivity	1 meta-analysis of 19 cross-sectional studies	25%	0.19, 0.32	Low
Specificity	1 meta-analysis of 19 cross-sectional studies	94%	0.92, 0.96	Low

CI, confidence interval; *FPG*, fasting plasma glucose; *HbA_{1C}*, hemoglobin A_{1C}.

The certainty of evidence however for the studies retrieved the diagnostic accuracy of HbA_{1C} and FPG as screening tests for prediabetes were graded as low due to risk of bias due to unclear sampling strategy and indirectness.

4.3.4. Cost Implication

Screening for both impaired glucose tolerance and diabetes is cost-effective. Targeted screening of high-risk groups is more cost-effective than universal screening.[71] A 2014 cost-effectiveness simulation study[72] has postulated avoidance of about $124,600 and $91,200 in lifetime medical expenditures if a new case of diabetes is prevented at age 40 and age 50 years respectively. Locally, no available studies have investigated this matter.

4.3.5. Equity, Acceptability, and Feasibility

Currently, no data is available on Filipino adults' values and preferences including equity and acceptability of available prediabetes screening modalities. Most available studies have included issues on diabetes care programs in the country. These issues can be indirectly attributed to prediabetes screening due to the similarities in diagnostic tests and treatment modalities advocated. Diabetes care in the Philippines is disadvantaged and challenged with respect to resources, government support, and economics. The national insurance system does not cover comprehensive diabetes care in a preventive model and private insurance companies only offer limited diabetes coverage. A major concern for Filipinos is the high cost of laboratory procedures which are mostly "out-of-pocket" expenses in the country. Diabetes as being mostly "out-of-pocket" now translates to poor pharmacotherapy impairing prevention of complications.[73]

4.3.6. Recommendations from Other Groups

The US Preventive Task Force Services in 2021 have recommended the screening for prediabetes and type 2 diabetes among nonpregnant adults groups aged 35–70 years who have overweight or obesity and have no symptoms of diabetes. Based on recent data showing that the incidence of prediabetes and diabetes increases at age 35 and the evidence on the benefits of early interventions for those diagnose of the disease, the task force has lowered the age cut-off for screening to 35 years from 40 years as recommended in the 2015 guideline. Screening intervals every 3 years were recommended and deemed reasonable for adults with normal blood glucose levels on screening. Patients who will be diagnosed with prediabetes will be referred or offered referral to effective preventive interventions.[66]

The American Association of Clinical Endocrinologists in 2022[74] and the American Diabetes Association in 2023[59] recommended the universal screening for prediabetes and diabetes for adults 45 years or older, regardless of risk factors and screening adults who are overweight or obese with 1 or more risk factors, regardless of age. The recommended repeat screening is at a minimum of 3-year intervals if test results are normal. The recommended laboratory tests to be used are FPG level, OGTT and HbA1C level.[59, 74]

The UNITE for Diabetes Philippines in 2014[75] has recommended that all individuals seen at any physician's clinic should be evaluated annually for risk factors for type 2 diabetes and prediabetes. It is recommended that in the presence of any of the risk factors for type 2 diabetes mentioned in the guideline should prompt the physician to order laboratory testing for diabetes and pre-diabetes. Universal screening using laboratory tests however is not recommended as it would identify very few individuals who are a risk. Repeat testing should be done annually if initial tests are negative.[75]

4.4. Estimated Glomerular Filtration Rate, Urine Albumin-creatinine Ratio, Urine Albumin Concentration, and Kidney Ultrasonography in Screening for Chronic Kidney Disease

RECOMMENDATIONS

1. **Among apparently healthy, asymptomatic adults, we suggest against routine screening for chronic kidney disease (CKD) using estimated glomerular filtration rate (eGFR) computed with CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation.**
   (weak recommendation, low certainty evidence)

2. **Among apparently healthy, asymptomatic adults, we suggest against routine screening for CKD using urine albumin-creatinine ratio (UACR) or urine albumin concentration (UAC).**
   (weak recommendation, low certainty evidence)

3. **Among apparently healthy, asymptomatic adults, we suggest against routine screening for CKD using kidney ultrasonography**
   (weak recommendation, low certainty evidence)

Justification and Considerations

The estimated glomerular filtration rate (eGFR) computed using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation has been validated in Filipinos. The equation is not meant to be used if acute kidney injury is suspected. Primary care providers are advised to compute for the eGFR in the outpatient setting, and not interpret creatinine results independently. Urine albumin-creatinine ratio (UACR) is more widely available than urine albumin concentration (UAC) and is more convenient for patients in that only a spot sample is submitted. Routine screening for CKD with eGFR computation, UACR or UAC, and kidney ultrasonography is not advised in the absence of risk factors. Routine screening for CKD among apparently healthy, asymptomatic adults without risk factors is not cost-effective.

4.4.1. Burden of disease

The Kidney Disease: Improving Global Outcomes (KDIGO) in 2005 defined CKD as as kidney damage or glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for three months or more, irrespective of cause.[76] In many of the causes of CKD, kidney damage is ascertained by significant albuminuria, defined by KDIGO as an albumin excretion rate (AER) of ≥30 mg/day, which is equivalent to UAC ≥20 mg/L or UACR ≥30 mg/g.[77]

Disease Frequency

Chronic kidney disease is emerging to be a significant public health concern. While its prevalence is 9.1% worldwide, CKD is among the top 10 leading causes of death and disability.[11, 78] With the increasing health burden imposed by CKD, there is a need to

investigate the merits of developing sustainable and equitable CKD identification programs for Filipinos.

Natural History of the Disease

Initially, CKD presents with signs of kidney damage such as albuminuria. If progressive, CKD can lead to a decline in kidney function. When severe, clinical manifestations may include volume overload, hyperkalemia, metabolic acidosis, hypertension, anemia, and mineral and bone disorders. In its most severe form, CKD results in the different clinical manifestations of the uremic syndrome. Ultimately, CKD leads to renal failure, necessitating renal replacement therapy. CKD is also associated with CV complications, which are the most common cause of death among CKD patients.[79]

Management of the Disease

Aside from determining and managing the cause of CKD, optimal management of CKD includes CV risk reduction, treatment of albuminuria, avoidance of nephrotoxins, and adjustment to drug dosing. If applicable, CV risk reduction is managed with optimal blood pressure control, if applicable, and the use of statins. Complications of CKD, such as hyperkalemia, metabolic acidosis, hyperphosphatemia, vitamin D deficiency, secondary hyperparathyroidism, and anemia must also be managed. Referral to a nephrologist should be done in persons at high risk of CKD progression, such as individuals with an eGFR of less than 30 mL/min/1.73 m^2, albuminuria ≥300 mg per 24 hours, or rapid decline in eGFR. Renal replacement therapy with hemodialysis, peritoneal dialysis, or kidney transplantation may ultimately be needed.[80]

Economic Impact of the Disease

CKD carries a very high cost of care: funding for kidney replacement therapies alone accounted for the 2nd largest expense of the Philippine Health Insurance Corporation.[81, 82] Interventions to slow kidney disease progression are available.[83] In populations at risk, early recognition and intervention can substantially affect public health outcomes.[84]

4.4.2. Benefits and Harms of Screening Tests

A systematic review[85] did not find any conclusive evidence on the benefits of albuminuria screening in the general population, whether via UAC or spot UACR. Furthermore, the review found no evidence of harm associated with microalbuminuria screening because none of the included studies reported it.[85] Another review[86] suggested that more studies are needed to investigate the safety outcomes of screening that are important to patients. Potential harms from screening include anxiety from a positive test, the loss of income from days spent undergoing further work-up and monitoring, delays in receiving treatment after a positive result, and false assurance about health status from false negative results.

All-cause Mortality, Renal Failure, and Cardiovascular Risk

A sub study[86] (n = 864) of the Prevention of Renal and Vascular Endstage Disease (PREVEND) study, a prospective community-based study in the Netherlands that involved 5,925 patients, that screened for albuminuria in the general Dutch population suggested that UAC screening detected CKD patients who had accelerated renal function loss and increased CV risk compared to subjects without CKD. A controlled study[87] of the screening program among the Australian Aboriginal community compared to

historically matched controls showed that treatment with perindopril may reduce deaths and renal failure. A randomized control trial[88] that was another sub study of the PREVEND trial showed that screening the general population and treating albuminuric subjects with angiotensin-converting enzyme (ACE) inhibitors may have a trend to benefit in terms of lower CV risk. The characteristics of the included studies are found in the Appendix 10.2.

4.4.3. Diagnostic Performance of Screening Tests

Urine Albumin Concentration and Urine Albumin-Creatinine Ratio

Two observational studies[89, 90], which involved 5,925 individuals from a prospective cohort community-based study in the Netherlands (PREVEND study) showed that the pooled sensitivity of the UAC ≥20 mg/dL compared to a diagnosis of CKD was 49% (95% CI [0.45, 0.53]), and the pooled specificity was 96% (95% CI [0.95, 0.96]). In one of the studies[87], the sensitivity of UACR was measured to be 49% (95% CI 0.41, 0.57), and specificity of 99% (95% CI [0.98, 0.99]) (table 9).

Table 9. Diagnostic Performance of Urine Albumin-Creatinine Ratio in the Diagnosis of Chronic Kidney Disease.

Test result	Number of Results per 1,000 Patients Tested (95% CI) Prevalence 9.1%	Number of participants (studies)	Certainty of Evidence
True positives	45 (52, 65)	153 (1)	Low
False negatives	46 (26, 39)		
True negatives	897 (893, 901)	2374 (1)	Low
False positives	12 (8, 16)		

CI, confidence interval.

Renal Ultrasonography

No studies that compared renal ultrasonography to conventional measures of renal function (glomerular filtration rate, albuminuria) to screen CKD in asymptomatic apparently healthy individuals were found.

4.4.4. Cost Implication

A sub study[88] of the PREVEND study showed a trend towards benefit in terms of cost-effectivity with screening the general population and treating albuminuric subjects with ACE inhibitors. Similarly, in a study[91] that looked at the cost-effectivity of screening ACR in a simulated CKD cohort based on the US Renal Data System data, microalbuminuria screening was cost-effective for patients with diabetes or hypertension but not for the general population.

However, analyses[92–94] of a recent systematic review do not show population-based screening for CKD to be cost-effective. Screening the general population using microalbuminuria to slow the progression of CKD and decrease mortality is not cost-effective unless performed at high-risk groups or at infrequent intervals. However, if done among high-risk groups, screening for albuminuria is cost-effective.[95] These high-risk groups include people with diabetes, hypertension, or advanced age. Regarding maintaining low costs, UAC may be preferred over ACR as the screening method.[85]

No cost-effectivity studies that included kidney ultrasound to screen for CKD were found. Local studies for CKD screening with serum creatinine, UACR, and UAC are also lacking. The cost of these screening tools is summarized in table 10.

Table 10. Costing Data on the Different Screening Tests for Chronic Kidney Disease.

Parameter	UAC	UACR	Kidney Ultrasound
Unit cost of screening intervention	₱600.00	₱1,540.00[a]	₱800.00[b]

[a] https://djrmh.doh.gov.ph/rates-and-fees/laboratory-fees
[b] https://fnlghtc.doh.gov.ph/index.php/rate-and-fees/ultrasound-fees

4.4.5. Equity, Acceptability, and Feasibility

Equity

The complexity and chronicity of CKD require careful study and there is scarce data on these factors. Even in high-income countries, population-based screening has not been shown to be cost-effective.[92] In low- and middle-income countries (LMICs), access to CKD care remains to be an important barrier to implementing CKD screening.[96] Low-income countries have lower rates of repeat tests to confirm CKD, as well as lower rates of initiating interventions and availability of screening policies.[92] The burden of CKD disproportionally afflicts people from LMICs.[97] In the International Society of Nephrology Kidney Policy Forum Series that focused on Southeast Asia and Oceania[98], it was stated that a patient is 2–3 times more likely to die from CKD in the Philippines than in Cambodia despite a comparable disease burden. For a CKD screening program to be impactful in the Philippines, geographical, logistical, structural, and cost aspects should be carefully studied and considered to develop locally appropriate solutions.

Acceptability

There are currently no studies on the level of awareness or attitudes of Filipinos toward chronic kidney disease. A cross-sectional study[99] among community-dwelling Filipino adults revealed a high prevalence of non-communicable disease progression and insufficient awareness of preventive behaviors. It is essential to consider local customs and beliefs in designing a strategy for CKD screening and prevention.

Feasibility

The Philippines has around 3,900 primary care facilities, of which 2,593 are rural health units/health centers (RHU/HC). Only 50% of Filipinos have access to an RHU/HC within 30 minutes of travel time.[100] Tests for albuminuria and kidney ultrasound require specialized equipment unavailable in these primary care settings. Underinvestment in health is a major concern, and the Philippines needs significant and sustained investments to meet the projected need. A paradigm shift is required in order to substantially reduce the large health infrastructure gap that impacts integrated patient care for CKD.

4.4.6. Recommendations from Other Groups

There is currently no clear consensus on screening for CKD in the general population. There are no recommendations for screening for CKD in asymptomatic persons without risk factors. The US Preventive Services Task Force[101] concluded that the evidence on routine screening for CKD in asymptomatic adults is lacking, and that the balance of

benefits and harms cannot be determined. The UK National Screening Committee[102] and the American College of Physicians (ACP)[103] recommend against screening for this CKD, as there is no evidence that early identification through screening would be beneficial. UK NICE guidelines[104] recommend testing for proteinuria only in specific sub-groups with risk factors for CKD or indicators of CKD.

4.5. Serum Uric Acid in Screening for Hyperuricemia

RECOMMENDATION

Among apparently healthy, asymptomatic adults, we recommend against routine screening for hyperuricemia using serum uric acid.
(strong recommendation, low certainty evidence)

Justification and Considerations
A good history-taking and physical examination are mandatory during screening for disease. Hence, the panel made no recommendation on the use of history-taking and physical examination in screening for hyperuricemia. The panel gave a strong recommendation despite the low certainty of evidence due to consistency of results among the different studies and the absence of causality between levels of serum uric acid and clinical outcomes.

4.5.1. Burden of disease

Hyperuricemia is defined as serum uric acid more than 7 mg/dL and 6 mg/dL among men and pre-menopausal women, respectively.[12]

Disease Frequency

The prevalence of hyperuricemia as of 2015 in the Philippines was 25%.[12] Asymptomatic hyperuricemia or the absence of gouty arthritis or nephrolithiasis among those with hyperuricemia is present in 37.8% of males and 18% of females among adult Filipinos.[13]

Natural History of the Disease

Although hyperuricemia is a central feature of gout, elevated uric acid does not always result in the development of gout.[105] Gouty arthritis has a prevalence of 0.5% according to the National Nutrition Health Survey in 2013.[106] The incidence of gout up to five years has been shown to be increased among those with hyperuricemia.[107, 108] In a study of an outpatient clinic, two-thirds of patients with gout developed nephrolithiasis based on ultrasound findings.[109] Hyperuricemia and gout is closely related to the development of metabolic syndrome, in which another local study showed a 47.6% prevalence in patients with gout.[110] Hyperuricemia has also been shown to be associated with other disease such as hypertension, heart failure, coronary artery disease, atrial fibrillation, stroke, chronic kidney disease, and reduction in renal function.[111, 112] Aside from these, it is important to consider malignancy, lymphoproliferative diseases, and tumor lysis syndrome as causes of hyperuricemia.[113]

Management of the Disease

Asymptomatic hyperuricemia, in itself, does not require treatment. However, it is recommended to treat hyperuricemia in the following settings: Persons about to receive chemotherapy or radiation therapy for cancer, history of kidney stones, history of gout,

and persons with very high levels of serum uric acid (>12–13 mg/dL in men or >10 mg/dL in women).[113]

4.5.2. Benefits and Harms of Screening Tests

There were no direct studies that directly investigated the benefits of screening hyperuricemia by history and physical examination.

Estimated Glomerular Filtration Rate and Blood Pressure

Indirect evidence from a single open-label trial done involving 105 participants[114] on the treatment of asymptomatic hyperuricemia was the only study that assessed the benefits of screening using serum uric acid. In this study, participants with hyperuricemia and no known comorbidities (n = 32; allopurinol group) were randomized to intervention (allopurinol 300 mg/day for 4 months) or to placebo (n = 40; hyperuricemic control group), and were compared to a group of normouricemic participants (n = 33; normouricemic control group). After 16 weeks of intervention, there was decrease in serum uric acid level in the allopurinol compared to baseline, which were not seen in both hyperuricemic and normouricemic control groups. There was no difference in eGFR, systolic blood pressure, and diastolic blood pressure in the treatment arm between baseline and after 16 weeks. Other outcomes were not assessed in this trial.[114]

Safety Outcomes

In terms of harm, only indirect studies were retrieved, with 12 RCTs[115–126] on urate-lowering therapies (ULT) among asymptomatic hyperuricemia included (table 11). The studies included a total of 2,448 patients. Eight of the studies used allopurinol[115–119, 123–125] whereas four used febuxostat[120–122, 126] in their treatment arms. Eight of the studies were double-blind RCTs, four were done in the US[118, 119, 124, 125], one each in Kuwait[116], India[120], Japan[122] and Australia[123]. Two were single-blind, one each in Spain[115] and Japan[126]. The other two were open-label randomized trials, one each in China[117] and Malaysia[121].

Ten of the twelve trials recorded increases in liver enzymes as adverse event of ULT compared to placebo, but these did not reach statistical significance (table 11). Eight studies documented gastrointestinal symptoms, which also did not show statistical differences. Eight similar studies also documented worsening kidney function, CV events, and all-cause mortality, with no differences were observed in outcomes. Two studies evaluated for stroke and no differences were also noted. Ten studies also reported dermatologic side effects and there were almost similar in terms of number of outcomes. Overall, indirect evidence from 12 RCTs[115–126] investigating the use of allopurinol or febuxostat among asymptomatic hyperuricemic patients with comorbidities showed no significant difference in the adverse events investigated.

Table 11. Randomized Controlled Trials[115–126] Evaluating the Effects of Urate-lowering Therapies on Safety Outcomes.

Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Elevated liver function tests	10 RCTs (n = 1,667)	RR 1.29	0.71, 2.33	No difference	Very low

Gastrointestinal [a]	10 RCTs (n = 1,039)	RR 1.23	0.97, 1.57	No difference	Very low
Worsening kidney function	8 RCTs (n = 1,106)	RR 0.74	0.43, 1.29	No difference	Very low
CV events	8 RCTs (n = 1,106)	RR 0.87	0.68, 1.12	No difference	Very low
Stroke	2 RCTs (n = 460)	RR 0.51	0.16, 1.68	No difference	Low
Death	8 RCTs (n = 1,106)	RR 0.97	0.64, 1.47	No difference	Very low
Dermatologic	10 RCTs (n = 994)	RR 1.04	0.66, 1.62	No difference	Very low

[a] diarrhea, abdominal pain, nausea, and rash
CI, confidence interval; *CV*, cardiovascular; *RCT*, randomized controlled trial; *RR*, relative risk.

As mentioned, two studies[117, 121] were not blinded and were open-label and showed a high overall risk of bias. The first study[117] had a high risk for performance, detection, and attrition bias. The second study[121] had a high risk for performance and detection bias. The risk of bias summary is shown in the Appendix 10.3. All studies have at least one unclear bias issue based on their methodologies.

4.5.3. Diagnostic Performance of Screening Tests

There were no studies that compared serum uric acid to other tests for hyperuricemia.

4.5.4. Cost Implication

There are no local cost-effectiveness studies in screening for hyperuricemia among asymptomatic healthy individuals. The cost of consultation, laboratory tests, and ULT are summarized in table 12.

Table 12. Costing Data in Screening for Hyperuricemia.

	Cost in ₱
Symptom Check	
Consultation	500–1,000 per visit
Laboratory Testing	
Serum uric acid [a]	115
Urate-lowering Therapies [b]	
Allopurinol	8.75 per 100 mg tab 18.25 per 300 mg tab 262.50–547.50 per month
Febuxostat	15.00 per 20 mg tab 22.00 per 40 mg tab 450.00–660.00 per month

[a] price from Philippine General Hospital Outpatient Department
[b] price from Watson's Drugstore

4.5.5. Equity, Acceptability, and Feasibility

There were no studies retrieved on patient's values, preference, equity, acceptability, and feasibility. It can still be beneficial since it will detect hyperuricemia among low socio-economic class and may give interventions to avoid complications related to hyperuricemia. It is acceptable since this is a standard blood test that can be incorporated with other blood chemistries. Feasibility will depend on the capability of a locality or a health care facility.

4.5.6. Recommendations from Other Groups

The American College of Rheumatology, Philippine Rheumatology Association, Asia Pacific League of Associations for Rheumatology, and European League against Rheumatism all recommend against routine initiation of ULT for asymptomatic hyperuricemia (table 13).

Table 13. Recommendations from Other Groups on the Use of Serum Uric Acid in Screening for Hyperuricemia.

Group or Agency	Recommendation
American College of Rheumatology (2020)[127]	Initiating ULT is conditionally recommended *against* in patients with asymptomatic hyperuricemia Strength: Strong Certainty of evidence: High
Philippine Rheumatology Association (2008)[105]	In the general population, asymptomatic hyperuricemia should *not* be routinely treated with allopurinol. Well-known associated risk factors of hyperuricemia, ie. dyslipidemia, obesity, metabolic syndrome, psoriasis, malignancies, congestive heart failure, should foremost be addressed. Strength: None Level of evidence: C
Asia Pacific League of Associations for Rheumatology (2021)[128]	Among patients with asymptomatic hyperuricemia and hypertension, we recommend against urate-lowering therapy to reduce the risk of MACE or mortality (cardiovascular and all-case). Strength: Strong Certainty of evidence: Very low Among patients with asymptomatic hyperuricemia and CKD, there is insufficient evidence to recommend for or against ULT to reduce of mortality, MACE, or to prevent progression to end-stage kidney disease. Strength: None Certainty of evidence: Very low
European League Against Rheumatism[129]	The diagnosis of gout should not be made on the presence of hyperuricemia alone. Strength: None Certainty of evidence: Low

4.6. Anthropometric Measurements in Screening for Malnutrition

RECOMMENDATIONS

1. **Among apparently healthy, asymptomatic adults, we suggest screening for central obesity using waist circumference (WC).**
   (weak recommendation, low certainty evidence)

2. **Among apparently healthy asymptomatic adults, we suggest screening for central obesity using waist-hip ratio (WHR).**
   (weak recommendation, low certainty evidence)

3. **Among apparently healthy, asymptomatic adults, we suggest against screening for malnutrition using mid-upper arm circumference (MUAC).**
   (weak recommendation, low certainty evidence)

4. **Among apparently healthy, asymptomatic adults, we recommend routine screening for obesity using body mass index (BMI).**
   (strong recommendation, low certainty evidence)

Justification and Considerations

Increased waist circumference (WC), waist-hip ratio (WHR), and body mass index (BMI) are associated with increased all-cause and cardiovascular mortality and development of type 2 diabetes mellitus. BMI can readily be computed from an individual's height and weight. Although the evidence presented shows the outcomes for BMI as a continuous variable, the panel adapts the recommendation in PHEX1 in using the Asia-Pacific classification as more appropriate for the local setting, with obesity being classified as BMI of 25 kg/m^2 or higher. Routine screening for obesity is cost-effective.

4.6.1. Burden of disease

Malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. BMI is a simple screening tool, feasible in primary care settings, and accepted as a standard for assessing nutritional status among adults globally using only two simple metrics which are weight and height. However, BMI has limited capacity to accurately diagnose excessive fat accumulation or to discriminate between body fat and lean mass, hence waist and hip circumferences are measured for central obesity/adiposity. The use of BMI alone may not capture central adiposity which has a significant role in assessing metabolic and mortality risks.[130] Waist circumference is measured to provide an indicator of intra-abdominal adipose tissue, while waist-hip ratio is determined for fat distribution. For mid-upper arm circumference, this can be used as an alternative for BMI among immobile individuals or those with edema, or during emergencies for children.[131] However, a standard MUAC cut-off that can classify under- and overnutrition among adults has yet to be established. Other measures of nutritional status are more precise or accurate, but these are not feasible in primary setting, like the

use of bioelectrical impedance analysis and dual x-ray absorptiometry, unlike these anthropometric measures that are simple, and most of which require one measurement only.

An assessment of the etiology of weight gain and obesity is needed, and this may include additional medical history including age at onset of weight gain, events associated with weight gain, previous weight loss attempts, change in dietary patterns, history of exercise, current and past medications, and history of smoking cessation and its associated health risks, to plan for its treatment and obesity management strategies.

Disease Frequency

Globally, more than 1.9 billion or 39% of adults were overweight and 650 million of these or 13% were obese.[132] Asia and the Pacific region is home to the largest absolute number of overweight and obese people with prevalence of 40.9% in 2013.[133] In the Philippines, the prevalence of overweight and obesity among adults, increased more than two-fold since 1993. The rate significantly increased to 36.6% in 2018–2019, and 8.8% of these were obese.[10] The rates for central obesity based on waist circumference and waist-hip ratio were also high.[10, 134] Furthermore, the prevalence was significantly higher among women than in men[10] and obesity will be of great concern in LMICs by 2030[135]. On the other hand, there were 462 million adults who were underweight or those suffering from chronic energy deficiency globally.[136] The rate has been steadily declining since 1993 in the Philippines and the percentage of adults with chronic energy deficiency was 8.4% in 2018–2019.[10]

Natural History of the Disease

Obesity is a risk factor for many illnesses. Weight-related complications that are either caused or exacerbated by excess adiposity include the other components of the metabolic syndrome (prediabetes and type 2 diabetes, dyslipidemia, hypertension), cardiovascular disease, nonalcoholic fatty liver disease and nonalcoholic steatohepatitis, polycystic ovarian syndrome, female infertility, male hypogonadism, obstructive sleep apnea, reactive airway disease, osteoarthritis, urinary stress incontinence, gastroesophageal reflux disease, and depression.[137]

Management of the Disease

Management of obesity includes weight loss and screening for and managing weigh-related complications. Lifestyle therapy is first-line for weight loss, and this includes meal plans to reduce caloric intake, physical activity, and behavioral modifications. Pharmacotherapy for chronic weight management includes oslistat, phentermine/topiramate, naltrexone/bupoprion, and glucagon-like peptide-1 receptor agonists. Metabolic surgery is recommended for individuals with BMI 40 kg/m^2 and above or 35 kg/m^2 and above if with severe obesity-related complications.[137]

Economic Impact of the Disease

The economic impact of obesity comes from direct and indirect costs and accounts for a big percentage of the health care system and societal costs which can further exceed if no strategic interventions were implemented.[138] Household income, economic growth as

well as productivity would weaken because of obesity.[139] In 2019, the impact of overweight and obesity on gross domestic product (GDP) globally is estimated to be at 2.19% loss across countries. In the LMICs, which the Philippines belongs to, the impact of overweight and obesity translated to a loss of 1.26% or about $28 per capita. If the prevalence of overweight and obesity continue to increase, its impact on the global economy is predicted to increase to 3.29% of GDP by 2060.[140]

It has also been reported that the direct cost of obesity as percentage of national nominal GDP in the Philippines was between 0.16% to 0.32%, however, only the medical practitioner or consultation costs were covered in this estimate, which underestimates the actual cost of obesity.[139] Based on a theoretical scenario, the total cost of obesity in 2016 in the Philippines due to the increase in prevalence may lie between $3–6 billion. In 2019, the economic impact of overweight and obesity in the Philippines was approximately $5.06 billion, corresponding to 1.3% of GDP and $47 per capita. A big portion of this total cost in the country was from indirect costs (89.7%). Furthermore, it was forecast that the economic impact of the disease will increase to $84.58 billion by 2060 which is equal to $563 per capita and 4.5% of GDP.[141]

In the workforce, obesity was reported to be associated with absenteeism and presenteeism. Among obese individuals, the cost of absenteeism ranged from $108-1,857, while presenteeism costs $11-4,175.[142]

The Philippine government allocated a large fraction of expenditure to address the problem of obesity in the country. In a recent review of public expenditures for nutrition in national government agencies in the Philippine, the total spending for the management and prevention of overweight and obesity alone is reported to be ₱919.2 million in 2017-2019.[143]

4.6.2. Benefits and Harms of Screening Tests

All studies reviewed were indirect since there were no studies found comparing those who were screened with anthropometric measures against those who were not screened, with outcomes of all-cause mortality, cardiovascular mortality, myocardial infarct, quality of life, diabetes, or hypertension. Moreover, all the studies included are mostly cohort studies.

For indices of central obesity, four studies[144–147] that included more than 25 million participants were retrieved (table 14). Two SRMA of cohort studies had the general population, never smokers, and healthy never smokers as participants.[144, 145] One cohort study[147] of NHANES III recruited adults with BMI >18.5 kg/m2 without history of non-skin cancer, and one 10-year cohort study[147] from Iran recruited adults with and without diabetes.

Various anthropometric indices for overweight and obesity were compared, and particularly included studies that reviewed WC and WHR. All-cause mortality (including total mortality)[145], cardiovascular mortality[146], and diabetes[145, 147] were the outcome measures included, with follow-up duration of less than 5 years to more than 20 years for all-cause mortality and diabetes, and mean follow-up of 14.3 years for cardiovascular

mortality. As interventions were non-invasive, all four studies[144–147] reported no adverse outcomes.

For body mass index, one systematic review and dose-response meta-analysis[145] of 182 cohort studies with over 5 million participants was retrieved. Participants (men and non-pregnant women) were mostly from North America, Europe, and the Far East, while few were from South Asia, Southeast Asia, Middle East, Australia, South America, and Africa. Outcomes measured in this study was the risk of type 2 diabetes in relation to general or central adiposity and body fat content using different anthropometric measures of adiposity including BMI. The characteristics of cohort studies included in the meta-analysis of anthropometric measures and risk of type 2 diabetes can be accessed in the study's data supplement.[145] The study had risk of bias, indirectness, inconsistency or high heterogeneity, and publication bias, hence the certainty of evidence was low. However, upgrades were noted for dose-response gradient and relatively large effect size. The risk of bias summary is shown in Appendix 10.4.

All-cause Mortality

Based on one SRMA[144], indices of central fatness (WC and WHR), showed positive and significant association with a higher risk for all-cause mortality (table 14). Overall, the HR for every 10 cm increase in WC for all-cause mortality was 1.11 (95% CI [1.08, 1.13]). Meanwhile, for every 0.1 unit increase in WHR, HR was 1.2 (95% CI [1.15, 1.25]).[144]

Table 14. Meta-analyses and Cohort Study on Evaluating the Effect of Screening for Malnutrition using Waist Circumference and Waist-hip Ratio on All-cause and Cardiovascular Mortality and Type 2 Diabetes Mellitus.[144–146]

Critical Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
All-cause mortality	50 studies for WC (n = 2,056,428)[144]	For every 10 cm increase in WC		Benefit	Low
		HR 1.11	1.08, 1.13		
		HR 1.08 (men)	1.04, 1.13		
		HR 1.12 (women)	1.09, 1.16		
	31 studies for WHR (n = 1,112,816)[145]	For every 0.1 increase in WHR		Benefit	Low
		HR 1.20	1.15, 1.25		
		HR 1.16 (men)	1.09, 1.23		
		HR 1.21 (women)	1.16, 1.26)		
		Normal BMI and high WHR vs normal BMI and no central obesity			
		HR 1.87 (men)	1.53, 2.29		
		HR 1.48 (women)	1.35, 1.62		
Cardiovascular mortality	1 cohort study (n = 15,184)[146]	Normal BMI and high WHR vs normal BMI and no central obesity		Benefit	Very Low
		HR 1.78 (men)	1.23, 2.57		
		HR 2.25 (women)	1.66, 3.05		

BMI, body mass index; *CI*, confidence interval; *HR*, hazard ratio; *WC*, waist circumference; *WHR*, waist-hip ratio.

Cardiovascular Mortality

In the cohort study for cardiovascular mortality[146], high WHR showed to increase cardiovascular mortality risk despite having a normal weight. The risk of CV mortality in men with normal-weight and high WHR was reported to be 78% higher (HR 1.78, 95% CI [1.23, 2.57]). In women, the risk for CV mortality was twice higher compared to women with similar BMI but without central obesity (HR 2.25, 95% CI [1.66, 3.05]).[146]

Type 2 Diabetes Mellitus

Two cohort studies[145, 147] reported an association between high WC and risk of developing T2DM. Waist circumference was revealed to be the most crucial anthropometric measure to predict type 2 diabetes.[147] Every 10-cm increase in WC was associated with 61.0% higher risk for diabetes (RR 1.61, 95% CI [1.52,1.70]), and showed strong and linear association between higher WC and diabetes.[144] Meanwhile, each 0.1 unit increase in WHR was linked to 63.0% higher risk for diabetes.[145]

On the other hand, a higher BMI was associated with a higher risk of developing type 2 diabetes (table 15). It was reported that for every 5 kg/m^2 increase in the BMI, the risk of having diabetes was 72% higher (RR 1.72, 95% CI [1.65, 1.81]), revealing a strong and linear association between BMI and diabetes risk. Moreover, the risk was slightly higher among men (RR 1.75, 95% CI [1.64, 1.86]) than among women (RR 1.69, 95% CI [1.61, 1.79]).[145]

Table 15. Meta-analysis[145] on Evaluating the Effect of Screening for Malnutrition using Waist Circumference, Waist-hip Ratio, and Body Mass Index on Type 2 Diabetes Mellitus.

Critical Outcome	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Type 2 diabetes mellitus	78 studies for WC (n = 21,459,955)	For every 10 cm increase in WC		Benefit	Low
		RR 1.61	1.52, 1.70		
		RR 1.68 (men)	1.54, 1.82		
		RR 1.68 (women)	1.56, 1.81		
	34 studies for WHR (n = 934,589)	For every 0.1 increase in WHR		Benefit	Low
		RR 1.63	1.50, 1.78		
		RR 1.67 (men)	1.47, 1.90		
		RR 1.71 (women)	1.54, 1.90		
	182 cohort studies for BMI (n = 5,585,850)	For every 5 kg/m^2 increase		Benefit	Low
		RR 1.72	1.65, 1.81		
		RR 1.75 (men)	1.64, 1.86		
		RR 1.69 (women)	1.61, 1.79		

BMI, body mass index; *CI*, confidence interval; *RR*, relative risk; *WC*, waist circumference; *WHR*, waist-hip ratio.

4.6.3. Diagnostic Performance of Screening Tests

Mid-upper Arm Circumference

An individual participant data meta-analysis (IPDMA) of twenty (20) datasets of 13,835 adults, from Africa, South Asia, Southeast Asia, North America, and South America was retrieved.[148] The aim of this IPDMA was to determine if a global MUAC cut-off can be established to classify underweight in adults (men and non-pregnant women) or those with BMI less than 18.5 kg/m^2. The comparator employed in this study was BMI and there were no outcome measures included in this IPDMA.[148]

Since most of the cross-sectional studies on MUAC are on diagnostic abilities of this measure to assess nutritional status of adults, or on establishing cut-offs for underweight, or overweight and obesity, this IPDMA[148] is the most comprehensive study on the diagnostic performance of MUAC in determining underweight (table 16). The sensitivity is 84.1% (95%CI [0.74, 0.91]) and the specificity is 83.2% (95%CI [0.72, 0.91]) with wide CIs. Moreover, the setting or the population included in these studies were those that

would most likely use an established low MUAC cut-off: people living with human immunodeficiency virus and/or tuberculosis, low-resource and development settings and individuals at risk of undernutrition.[148] Therefore, indirectness and bias for populations with low BMI are evident. Hence the certainty of evidence is very low.

Table 16. Meta-analysis[148] Evaluating the Diagnostic Performance of Mid-upper Arm Circumference compared to Body Mass Index.

Pooled Analysis	Basis	Pooled Estimate	95% CI	Interpretation	Certainty of Evidence
Sensitivity	20 studies (n = 13,835)	84.1%	0.74, 0.91	Inconclusive	Very Low
Specificity	20 studies (n = 13,835)	83.2%	0.72, 0.91	Inconclusive	Very Low

CI, confidence interval.

4.6.4. Cost Implication

No direct evidence was available regarding the cost-effectiveness of malnutrition screening, although the impact of obesity in the Philippine economy was huge and costly. Only one systematic review study was retrieved that aimed to determine the cost of malnutrition screening procedure, however, limited data availability made it impossible to evaluate the cost of malnutrition screening.[149]

Equipment or tools used during anthropometric measurements should have high reliability and validity to ensure that the data acquired are precise to accurately identify individuals who are at-risk of malnutrition. In this context, equipment such as weighing scale, tape measure, and stadiometer are usually costly. For instance, a Seca double window digital weighing scale (model: Seca 874) costs ₱49,900, while a stadiometer (model: Seca 213) used for height measurement, and tape measure for waist and hip circumferences, and MUAC (model: Seca 203) cost ₱24,400 and ₱1,450, respectively. To ensure that the equipment are still in their standard performance, preventive maintenance, calibration, and repair are also implemented before and after usage which may cost ₱5,000. Costs of equipment and services related to maintenance, repair, and calibration were acquired from the Food and Nutrition Research Institute of the Department of Science and Technology.

Moreover, the measurer should be properly trained or have qualified experience to ensure correct use of equipment during screening to avoid measurement errors, thus, conducting training for inexperienced staff including the materials necessary during training will likely add to the expense for malnutrition screening.

4.6.5. Equity, Acceptability, and Feasibility

Obesity is usually associated with unhealthy lifestyle and behavior, and most individuals with this condition have experienced or suffered from stigma and stereotyping. Overweight and obese participants have low satisfaction with their body image based on BODY-Q Rasch-scores.[150]

In a critical review, fatness can be defined at a personal level, but it frequently relies on the general concept of societal norms or peer pressure.[130] Weight loss products such as slimming coffee, tea, and other nutritional supplements are often marketed to cater to people who aim to reduce their weight.[151]

From a healthcare perspective, the quality of patient-centered care and encounter with healthcare providers may be affected due to stress and other psychosocial factors caused by their experiences of discrimination and stigma, which in turn, increase their feeling of rejection, humiliation, or belittlement.[151] One study[152] that reviewed 44 articles reported that obese individuals had experienced being blamed and shamed by their family, friends, and had lack of support from healthcare providers with regards to their weight, which caused detrimental impacts on their psychological and mental health.

Obese individuals are also likely to become underachievers due to social stigmatization and discrimination, thus limiting their career choices, and affecting their ability to present their skills and talents.[130] In the workforce, productivity of individuals with obesity is also reduced by 4–9 years across countries within the Association of Southeast Asian Nations (ASEAN). In 2016, reduced productivity was highest in the Philippines among obese males (8–12 years) across ASEAN countries, while obese females had lost 0.3–5 productive years.[139]

Screening apparently healthy, asymptomatic adults is the primary step in identifying nutritionally-at-risk individuals at the earliest possible stage of development of the condition who may benefit from appropriate nutritional intervention. However, diagnosis can be influenced by the method or tool used during the screening process.[153] While BMI is a widely used indicator in identifying obese persons, it has limited capacity to accurately diagnose excessive fat accumulation, particularly for those with in-between BMI ranges.[154] The use of BMI alone may not capture body fat distribution which has a significant role in assessing metabolic and mortality risks. According to the critical review, correlation of BMI and mortality rates usually does not consider other factors like family history of illnesses, history of smoking, alcohol abuse, mental disorder, and occupation. Moreover, many people who are obese have no cardiovascular risk factors.[130]

Diagnosis and management of obesity should not be solely based on BMI, and other measurements of adiposity may be considered to further assess obesity risk.[154] In a systematic overview of 19 evidence-based guidelines, WC provided added information on the risk of developing long-term health problems related to obesity, however, it should not be utilized as a routine measure for diagnosing overweight and obesity.[155] Moreover, it has been revealed in another systematic review and meta-analysis that WC, together with BMI, has limitations when used for obesity screening.[156] In a cross-sectional study[157], WC had a modest correlation with visceral fat, while waist-hip ratio had a strong correlation with visceral fat, and can also be used to predict risks linked with noncommunicable diseases.

Meanwhile, MUAC is another simple, non-invasive method for assessing nutritional status that can be used as an alternative method for BMI among immobile individuals or those with edema.[131] However, a standard MUAC cut-off that can classify under- and overnutrition among adults has yet to be established. Several studies attempted to derive a cut-off for MUAC that will detect overweight and obesity in line with BMI and WC[131, 158], as well as derive MUAC cut-offs for undernutrition among adults.[159–161]

On the other hand, a mixed-method synthesis study[162] reported the barriers and facilitators to screening and treating malnutrition. It was reported that individuals feel hesitant in disclosing their dietary history due to the perceived notion that their diet be described as poor. Another was that some individuals were offended when they were told to be at-risk after screening, possibly due to their experience with the healthcare practitioner during screening or the poor way of relying the information on them.[162] A meta-analysis[163] comprising 25 studies reported that healthcare professionals doubted the understanding of their patients in terms of the health risks associated with obesity after assessment. Furthermore, they have also conveyed discomfort during obesity screening of the opposite sex such as taking measurements for WC, which was likewise felt by patients who preferred to be assessed by a healthcare provider of the same sex.[163]

4.6.6. Recommendations from Other Groups

Recommendations from other groups are summarized in table 17. All groups[164–168] cited recommended screening for overweight and obesity using BMI, and stated additional criteria for the measurement of other anthropometric indices, like waist-to-height ratio for NICE[164], and waist circumference for the USPSTF[165], consensus recommendations in South and Southeast Asia[166], the Canadian CPGs[167], and the American Heart Association (AHA)/ American College of Cardiology (ACC)/ The Obesity Society (TOS) guidelines[168].

Table 17. Recommendations from Other Groups on the Use of Anthropometrics in Screening for Malnutrition.

Group or Agency	Recommendation	Strength of Recommendation Certainty of Evidence	Additional Criteria
NICE (2014, updated in 2022)[164]	Recommends the use of BMI to measure overweight and obesity		Measure WHtR for those with BMI <35 kg/m^2. WHtR is a practical estimate of central adiposity.
USPSTF (2012, updated in 2018)[165]	Recommends screening of all adults for obesity using BMI	B recommendation	Refer patients with BMI of ≥30 kg/m^2 to intensive, multicomponent behavioral interventions. WC may be an acceptable alternative to BMI in some patient subpopulations.
Consensus recommendations for care and management of obesity in South and Southeast Asia (2023)[166]	Recommends measurement of BMI and to apply cut-off points adopted by each country		Measure waist circumference and apply the cut-off points adopted by each country, to confirm excess abdominal adiposity.
Canadian Adult Obesity CPGs (2020)[167]	Recommends the use of BMI in all adults	Level 2a, Grade B	Measure waist circumference in persons with a body mass index of 25-34.9 kg/m^2 (Level 2b, Grade B)
AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults (2013)[168]	Recommends measurement of height and weight, and determining BMI at annual visits or more frequently	Expert Opinion	Measure waist circumference at annual visits or more frequently in overweight and obese adults (Expert Opinion)

ACC, American College of Cardiology; *AHA*, American Heart Asssociation; *BMI*, body mass index; *CPG*, clinical practice guideline; *NICE*, National Institute for Health and Care Excellence; *TOS*; The Obesity Society; *USPSTF*, United States Preventive Services Task Force; *WC*, waist circumference; *WHtR*, waist-to-height ratio.

4.7. Hemoglobin and Red Blood Cell Parameters in Screening for Nutritional Anemia

RECOMMENDATION

Among apparently healthy, asymptomatic adults, we recommend screening for nutritional anemia using hemoglobin and red blood cell (RBC) parameters. ***(strong recommendation, low certainty evidence)***

Justification and Considerations

The recommendations stated here only covers nutritional anemia and excludes screening for other causes of anemias, such as anemia from blood loss, anemia of inflammation, hemoglobinopathies, and other genetic causes of anemia. Although the certainty of evidence is low, the panel recommended screening for nutritional anemia because of the high prevalence of anemia, especially in women and in the elderly. The evidence presented included women 20–39 years old and men younger than 60 years, the panel still recommends the use of hemoglobin and red blood cell (RBC) parameters given the prevalence of anemia among Filipinos and benefit with micronutrient supplementation. Only hemoglobin and RBC parameters are needed in screening for anemia, and these tests are often part of CBC in most laboratories.

4.7.1. Burden of disease

Anemia is a hematologic condition where there is a reduction in the hemoglobin content, size, and/or number of RBCs; in practical terms, this is indicated by a hemoglobin concentration below a specific cut-off point for an individual's age, gender, physiological status, and even altitude of location. Anemia can result from 1) a decrease in RBC production, 2) an increase in RBC destruction (ex. anemia from malaria), and/or 3) blood loss. An anemia is considered nutritional in origin when one or more nutrients essential to RBC formation is deficient, and replacement of that specific nutrient will correct the anemia. The World Health Organization (WHO) defines anemia in non-pregnant women as having a hemoglobin concentration of <120 g/L.[169] World Health Organization estimates for 2019 showed that up to 29.9% of women aged 15–49 years old suffered from anemia.[170] Another emerging population group of concern for anemia is the elderly population, where the prevalence varies between 10–45%, and can be ascribed to various etiologies.[171] Although there has been some debate about the appropriate thresholds for anemia in the elderly, most publications still use the WHO criteria of <12 g/dL for women and <13 g/dL for men in the general population to capture anemia in the elderly adult.[172]

Disease Frequency

The Expanded National Nutrition Survey 2019[10] results showed that the prevalence of anemia among adults aged 20-59 years old in the Philippines has been steadily decreasing from 9.3% in 2013 down to 7.2% by 2019. However, the 2019 prevalence of anemia among women in this group, 10.0%, was more than double of men at 4.3%. Anemia among the Filipino elderly also decreased from 20.8% in 2013 to 16.9% in 2019,

but with a less significant difference between sexes. Up to 17.4% of elderly Filipino men were anemic as opposed to 16.6% of elderly Filipino women. [10] A 2018 study[173] conducted by Food and Nutrition Research Institute found that iron-deficiency was still the most prevalent cause of anemia in the National Capital Region (NCR), affecting up to 37.6% of anemic individuals studied. The treatment of iron-deficiency anemia (IDA) is very accessible and cheap; hence, the usual practice is to treat all anemias as IDA without screening. However, this same study also found that the prevalence for non-nutritional anemias, specifically those associated with thalassemia and other hemoglobinopathies was up to 27.8% in this population group. These non-nutritional anemias will not respond to micronutrient therapy for anemia.[174] Given the above prevalence of hemoglobinopathies, at least in NCR, it now becomes important to screen and differentiate between nutritional and non-nutritional anemias in order to initiate the most appropriate course of treatment, and prevent harm related to iron overload and other sequelae of inappropriate micronutrient supplementation.

4.7.2. Benefits and Harms of Screening Tests

Four observational cohort studies[174–177] with a total of 1,779,861 participants, one small RCT[178] with 45 participants in a repeated measures design, and one meta-analysis[179] including 102 studies were retrieved.

Two of the cohort studies were situated in Korea, and focused on women aged 20-39 years old[174], and on selected individuals aged 40 years and above from the National Health Insurance Service–National Health Screening Cohort[175]. Outcome measures considered in these studies included all-cause mortality reduction, mortality due to acute myocardial infarct, and mortality due to cardiovascular diseases. These studies used similar methodologies of baseline hemoglobin determination, followed by correction, subsequent determination over a period of 2–10 years, and follow up on outcomes.[174, 175]

The two remaining cohort studies[176, 177] and the small RCT[178] were used to assess benefits and harms from either phlebotomy or linked therapies such as iron replacement. One cohort study[176] on vasovagal syncope with phlebotomy focused on 677,956 patients aged 2 years old and above in Japan. Another cohort study[177] on leukopenia and infections from iron replacement therapy included 1,567 women of reproductive age in Qatar. All these patients were from a hematology clinic and undergoing intravenous iron therapy.[177] The small RCT[178] included 45 women of reproductive age in the US. Outcomes for this RCT included stress responses such as cortisol measurements, heart rate variability, and self-reported psychological stress while undergoing fingerstick and conventional venipuncture methods.[178]

The meta-analysis[179] of 102 studies gathered cohorts from various locations worldwide, with unknown total populations. It could not be ascertained if there was an overlap of studies used per RBC index considered, or if overlapping cohorts were assessed for different RBC indices.[180]

All-cause Mortality, Cardiovascular Mortality, and Mortality due to Acute Myocardial Infarction

The cohort studies showed that correction of anemia reduced all-cause mortality among young women (HR 0.81, 95% CI [0.69, 0.94]) (table 18). This effect was also observed but not deemed significant for reducing mortality due to acute myocardial infarction (AMI) (HR 0.92; 95% CI 0.59, 1.44).[174] Correction of anemia among men also reduced all-cause mortality with an (adjusted HR 0.67, 95% CI [0.59, 0.77]). Correction of anemia was not seen to have a significant effect on reduction of mortality due to AMI (adjusted HR 0.71, 95% CI [0.35, 1.42]) or other CV mortalities in men (adjusted HR 0.75; 95% CI 0.52, 1.07).[175] In this same cohort[175], the same trend was seen among older women but was deemed less significant.

Table 18. Cohort Studies[174, 175] Evaluating the Effect of Treatment of Nutritional Anemia on All-cause Mortality, Cardiovascular Mortality, and Mortality due to Acute Myocardial Infarction.

Critical Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
All-cause mortality	1 cohort study[174] (n = 678,798 young women)	HR 0.81	0.69, 0.94	Benefit	Very low
	1 cohort study[175] (n = 4,538 men)	HR 0.67	0.59, 0.77	Benefit	Very low
CV mortality	1 cohort study[175] (n = 4,538 men)	HR 0.75	0.52, 1.07	Inconclusive	Very low
Mortality due to AMI	1 cohort study[174] (n = 678,798 young women)	HR 0.92	0.59, 1.44	Inconclusive	Very low
	1 cohort study[175] (n = 4,538 men)	HR 0.71	0.35, 1.42	Inconclusive	Very low

AMI, acute myocardial infarction; *CI*, confidence interval; *CV*, cardiovascular; *HR*, hazard ratio.

Safety Outcomes

Safety outcomes of screening for nutritional anemias are outlined in table 19. Determination of hemoglobin and RBC parameters necessitates phlebotomy. A risk associated with phlebotomy is the occurrence of vasovagal syncope (VVS). VVS is a common form of reflex syncope, or a transient loss of consciousness due to failure of blood pressure autoregulation. A retrospective cohort study[176] of patients who underwent outpatient phlebotomy for various indications showed 27 incidences of VVS. In this cohort[176], VVS was more associated with the use of 5 or more blood collection tubes or a waiting time of 15 minutes or more for phlebotomy.

Table 19. Cohort Studies[176–178] Evaluating the Safety of Treating Nutritional Anemias.

Safety Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Stress response to phlebotomy	1 RCT[178] (n = 45)	Not calculated	—	Inconclusive	Very low
Vasovagal response to phlebotomy	1 cohort study[176] (n = 677,956)	Not estimable	Not estimable	Inconclusive	Very low
Leukopenia with iron replacement therapy	1 cohort study[177] (n = 1,567)	Not estimable (30 events)	Not estimable	Inconclusive	Very low

CI, confidence interval; *RCT*, randomized controlled trial.

Even in the absence of VVS, patients may experience stress responses during phlebotomy, especially with the use of conventional venipuncture methods. It has been thought that the use of smaller needles such as in the fingerstick method for Hgb measurement, may decrease the risk of stress responses. However, a small trial in 45 women of reproductive age showed that stress responses such as cortisol

measurements, heart rate variability, and self-reported psychological stress were equivalent for both venipuncture and fingerstick methods for blood collection.[178]

One risk associated with parenteral iron replacement therapy is leukopenia even in the absence of infection or other comorbidities. A cohort study of patients who received parenteral iron replacement therapy showed 30 instances of leukopenia among patients with previously normal white blood cell counts. This adverse event was deemed as having limited clinical significance in this cohort.[177]

No studies were found on oral iron replacement therapy, or on vitamin B replacement therapy or supplementation for patients with anemia but without comorbidities.

4.7.3. Diagnostic Performance of Screening Tests

Red Blood Cell Morphology and M/H Ratio

In terms of diagnostic performance, the meta-analysis[179] showed that the diagnostic indices currently being used have sensitivities ranging from 63% to 92%, and specificities from 52% to 86% for differentiating IDA from thalassemia trait (table 20). M/H ratio (calculated as the percentage of microcytic RBCs over the percentage of hypochromic RBCs) has the highest sensitivity (92%) and specificity (86%) compared to other indices used in work-up for iron deficiency anemia versus thalassemia.[179]

Table 20. Meta-analysis[179] Evaluating the Diagnostic Performance of RBC Morphology and M/H Ratio in Differentiating Iron-Deficiency Anemia from Thalassemia.

Pooled Analysis	Basis	Pooled Estimate	95% CI	Certainty of Evidence
RBC Morphology				
Sensitivity	102 studies	Varies by index	0.63, 0.92	Low
Specificity	102 studies	Varies by index	0.52, 0.86	Low
M/H ratio				
Sensitivity	15 studies (n = 3,091)	87%	0.26, 0.98	Low
Specificity	15 studies (n = 3,091)	81%	0.59, 0.99	Low

CI, confidence interval; *RBC*, red blood cell.

4.7.4. Cost Implication

In the Philippines, hemoglobin determination and RBC parameters are part of complete blood count (CBC) routine tests (table 21). These may be done on an outpatient basis, but also form part of routine in-patient workups. Confirmatory testing is usually done with serum ferritin.[180, 181]

Table 21. Costing Data in Screening for Nutritional Anemia.

Parameter	Cost in ₱
CBC (outpatient)	120–250
CBC (inpatient)	210
Ferritin (inpatient)	2,450

CBC, complete blood count.

4.7.5. Equity, Acceptability, and Feasibility

There are no studies in the Philippines or Southeast Asia specifically covering patients' values and preference, or the equity and acceptability of anemia screening modalities in

the adult population, or outside of antenatal care or preoperative settings.

Access to anemia screening, especially for women, may be impacted by normative gender beliefs concerning health and well-being. A study[182] in India showed that despite objectively poorer health status as assessed by medical examinations, women were more likely to self-report better health status than men. This may be attributed to differing expectations for good health, as well as common practices surrounding treatment (including but not limited to seeking healthcare from informal providers). This is seen to impact health-seeking behaviors, including anemia screening.[182]

Access to preventive measures against nutritional anemia have a great impact on target populations in middle and low-income countries. A study[183] of 18 LMICs showed that food fortification with iron has the potential to prevent 72.1 million cases of anemia among non-pregnant women of reproductive age in these settings. This translates to a 34% reduction in the number of cases of anemia and an annual reduction of 5.4 million disability-adjusted life-years among women and children receiving fortified foods.[183]

4.7.6. Recommendations from Other Groups

Recommendations from other groups are summarized in table 22. These organizations recommend confirmatory testing for IDA and testing for the cause of IDA.[184–186]

Table 22. Recommendations from Other Groups in Screening for Nutritional Anemia.

Group or Agency	Recommendation	Remarks
British Columbia Ministry of Health (Updated 2019)[184]	Recommended confirmatory testing for iron deficiency anemia and investigation of underlying causes in addition to screening with history, physical examination, and CBC parameters. Confirmatory test recommended for IDA: Serum ferritin	Tests to determine cause of IDA: Bidirectional endoscopy, testing for celiac disease and *Helicobacter pylori* No strength of recommendation included/ available
British Society of Gastroenterology (Updated 2021)[185]		
American Gastroenterological Association (2021)[186]		

CBC, complete blood count; *IDA*, iron deficiency anemia.

4.8. Tanner Staging in Screening for Differences in Timing of Sexual Maturity

RECOMMENDATION

Among apparently healthy, asymptomatic adolescents, we suggest against routine assessment of sexual maturity using Tanner staging.
(weak recommendation, low certainty evidence)

Justification and Considerations
Differences in timing of sexual maturity, such as pubertal delay and precocious puberty, affects quality of life and mental well-being of adolescents. Routine assessment for sexual maturity using Tanner staging is not supported by evidence. A disadvantage with routine Tanner staging is the discomfort associated with undressing.

4.8.1. Burden of disease

Adolescence is the period between childhood and adulthood where a lot of physical, cognitive, and social maturation, and even psychological development occurs.[187] Its beginning coincides with the onset of puberty and is characterized by drastic changes in physical appearance (physical growth, facial structure change, and development of secondary sexual characteristics) and hormone levels.[187, 188] This process often starts at age 8–14 years in females, and ages 9–15 years in males.[187]

Development of secondary sexual characteristics is assessed using Tanner method.[188] This method uses measurements of pubic hair development in both males and females and, breast development in girls, and genital development and testicular volume in boys, which needs to be done by a pediatrician. Voice break in males and menarche in females are other milestones of secondary sexual characteristics. Full assessment of the Tanner stage would call for a need to undress the child which often problematic leading the physicians to omit this specific part of the physical examination.[188, 189] The use of self-reporting of pubertal Tanner stage was later suggested, however, a 2006 cross-sectional study[188] involving 240 children found this to be unreliable.

Precocious puberty is defined as the development of secondary characteristics before age 8 years (or menarche before age 9) in girls or 9 years in boys, and its estimated overall incidence is said to be 1 in 5,000 to 1 in 10,000 children.[15] Earlier timing of puberty is gradually being reported among Japanese children.[189] In a population based cross-sectional study[15] involving 4,058 Chinese pupils in grades 1–3, the adjusted prevalence of precocious puberty by Tanner stage was 6.19–11.47% in girls and 3.26% in boys. Precocious puberty or early puberty may not always be associated with disease but would still require support from healthcare providers, and identification of a child with pathologic pubertal development may allow for earlier intervention leading to less discomfort, and improved height outcomes.[189, 190]

4.8.2. Benefits and Harms of Screening Tests

Two observational studies[188, 190] which included a total of 11,831 children aged 8 to 14 years were retrieved. The overall certainty of evidence is very low due to serious issues of indirectness and imprecision.

The first study[189], a 2019 prospective longitudinal study, investigated the association between pubertal timing or timing of the development of secondary sexual characteristics with the outcomes quality of life, sleep quality, mental health difficulties and overall health. Japanese school children (n = 9,492) at 7th grade, aged 12–13 years old, were asked about the timing of their development of secondary sex characteristics, i.e., voice break for males (Tanner stage 3 or 4), and menarche for females (Tanner stage 4 or 5). Children were grouped according to the timing of their development where those who develop at age 9–10 years will be assigned to Group 1, those who develop at age 10–11 years will be assigned to Group 2, age 11–12 years to Group 3 and age 12–13 years to Group 4.[189]

The second study, a 2020 cross-sectional study[191] done among children and adolescents in Brazil (n = 2,239) aged 8–14 years, explored the association between body adiposity and stages of pubertal development. Children were grouped according to their pubertal development stage. Those who were below the first tertile of age were included in the early pubertal development stage group, those at the second tertile or more were included in the late pubertal development stage, while those between the first and second tertile were included in the reference group or normal pubertal development stages. The outcome analyzed in this study is adiposity, more specifically, sum of the measure of four skinfold thickness, measures of triceps or calf skinfold thickness only, and waist circumference values.[191]

Quality of Life

Male children who developed secondary sex characteristics early (age 9–10 years) are sixfold more likely to have poor quality of life, as assessed using the Dartmouth Primary Care Co-Operative Project Questionnaires, compared to those who develop secondary sex characteristics at age 12–13 years (adjusted OR [aOR] 5.96, 95% CI [1.89, 18.86]).[189]

Sleep Quality

Male children who developed secondary sexual characteristics earlier (age 9–10 years) had poorer sleep quality, as assessed using the Pittsburg Sleep Quality Index, than those who developed and yet to develop at 12–13 years old (aOR 3.76, 95% CI [1.31, 10.82]). Female children who developed secondary sexual characteristics at age 10–11 years are more likely to have poorer sleep quality (OR 1.40, 95% CI [1.12, 1.75]) but after adjustment, the statistical significance was lost.[189]

Mental Health Difficulties

The risk of having mental health difficulties among boys who developed secondary sex characteristics at age 10–11 years is increased by 69% compared to those who developed at 12–13 years old, however this statistical significance is lost after adjustment for confounders (OR 1.69, 95% CI [1.03, 2.76]). Girls who develop secondary sexual characteristics at 9–10 years old were more likely to experience mental health difficulties

(aOR 1.54, 95% CI [1.02, 2.33]). Similarly, girls who develop later at age 10–11 years and age 11–12 years also had increased risk (aOR 1.55, 95% CI [1.22, 1.97]; aOR 1.31, 95% CI [1.06, 1.62]; respectively).[189]

Over-all Health

The risk of having poorer over-all health is almost threefold more likely among boys who develop secondary sex characteristics at 9–10 years old compared to those who develop at 12–13 years (aOR 2.85, 95% CI [1.05, 7.77]), wherea girls who develop earlier (9–10 years old) had higher risk of having poorer over-all health (aOR 1.50, 95% CI [1.02, 2.19]), compared to those who develop a little later (10–11 years old; aOR 1.26, 95% CI [1.00, 1.58]).[189]

Adiposity

In the second study[191], a higher adjusted prevalence ratio (aPR) for central obesity or waist circumference was observed in both males (aPR 2.21, 95% CI [1.12, 4.35]) and females (aPR 2.18, 95% CI [1.04, 4.57]) with early pubertal development stages compared to those with normal pubertal development stages.[191]

4.8.3. Diagnostic Performance of Screening Tests

There were no studies which compared Tanner staging to other tests for sexual maturity.

4.8.4. Cost Implication

There were no cost-effectiveness studies on the use of Tanner staging for assessment of sexual maturity among asymptomatic adolescents found in this search. Since this is a physical examination, the cost of a consult is relevant for screening.

4.8.5. Equity, Acceptability, and Feasibility

Tanner staging is performed by inspection for the sexual characteristics of individuals, however, several reviews stated that this may cause discomfort to children. It does not require any specialized machines or kits and is performed by inspection. It can be integrated to physical examination.

4.8.6. Recommendations from Other Groups

Currently, there are no other guidelines regarding routine assessment of sexual maturity using Tanner staging among asymptomatic adolescents.

5. Research Implications/Gaps

Many research questions from the identified clinical questions in this CPG were unanswered in terms of benefits and harms of screening, equity, applicability, and feasibility. Direct evidence is still lacking to aid in providing definite recommendations for screening certain conditions using the tests. As recommended by the consensus panel, most of the screening tools in this guideline deal with taking the appropriate history and physical examination such as VMS in menopause, risk factors and physical findings for hypocalcemia or hypercalcemia, risk factors for chronic kidney disease, history of gout or nephrolithiasis for hyperuricemia, and evaluating for differences in timing of sexual maturity. There are limited data on these tests.

Generating direct evidence (screening vs. no screening) may be difficult. Because of this challenge, in some instances, establishing the diagnostic performance of tests as indirect evidence can be adequate. However, specific tests' accuracy in detecting early diseases and preventing them from developing into a chronic or more severe state is still not investigated.

There have been cost-effectiveness studies available for screening the diseases included in this CPG, but most of them are conducted in Western countries. In some of the diseases, such as in prediabetes and obesity, there is abundance in data internationally which may be applied locally. There is a need to look at health economic data for the various diseases in this CPG.

Social science research also plays a vital role in examining the impact of the diseases. However, few qualitative studies were found to provide a holistic view of the impact of screening for some conditions. Qualitative studies can also provide information on motivators or determinants among the general population in participating in a screening program despite the probable harm of stigma and mislabeling afterward.

Examining needs and monitoring implementation of screening programs were also found to be not well-established even if, in some conditions, guidelines and programs are already in place. Perspectives and experiences of clinical practitioners and other stakeholders directly involved in screening programs are rarely reported in studies.

Many research questions emerged from collating the evidence for this CPG and can be explored further. Filling in these gaps can provide a clearer picture of the impact of screening programs using previously mentioned tests and may influence the recommendations for updating this guideline.

6. Dissemination and Implementation

Dissemination

A full copy of this document will be sent to the Department of Health for transmittal and publication. The Disease Prevention and Control Bureau will transmit copies of this CPG

to the Philippine Health Insurance Corporation (PHIC) and health maintenance organizations and nongovernment organizations involved in a periodic health examination. The recommendations and the evidence summaries will be also be posted in the different medical societies involved in the consensus panel, such as PAFP, PCP, PCEDM, and PSN.

The DOH planned to develop a simplified version of this CPG and made it available in the format that will be ready for reproduction and dissemination to the patients in different health care settings. It will also be available for interested parties who might visit the DOH website. The different medical societies may also include the guidelines in their own websites.

Implementation

The SC will develop a program of monitoring to determine the best practices of relevant stakeholders in terms of diagnosis and management of lung carcinoma. Monitoring the use of this CPG may also be a subject of research by interested parties.

7. Applicability Issues

The PHEX Task Force accentuates some caveats of this CPG using equity and applicability lenses. Comprehensive history taking, physical examination, and monitoring are essential parts of evaluating risk factors and the probability of developing diseases. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Although this CPG intends to influence the direction of health policies for the general population, it should not be the sole basis for recreating or abolishing practices that aim to improve the health conditions of many Filipinos, particularly those part of the workforce.

8. Updating of the Guidelines

The recommendations herein shall hold until such time that new evidence on screening, diagnosing or managing various risk factors and diseases emerges and contingencies dictate updating this Philippine Guidelines on Periodic Health Examination. This guideline will be updated after three (3) years.

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10. Appendices

10.1. Characteristics of Included Studies on Screening for High Climacteric Syndrome

Study ID	Patients (n)	Index Test	Reference Standard	Outcomes	Study Design
Shin 2008[1]	Healthy, ovulatory and post-menopausal women with no endocrine disorders and no evidence of polycystic ovarian syndrome (n = 144)	FSH, LH, Estradiol, AMH, Inhibin B, IGF-1, IGFBP3	Unclear Data from pre-menopausal and post-menopausal women were compared and AUC was used to assess the ability of each marker to discriminate between the pre- and post-menopausal status.	LH >8.7 mIU/mL: Sn 98.2%, Sp 97%, *p* <0.001 FSH >22.3 mIU/mL: Sn 99.1%, Sp 97%, *p* <0.001 Estradiol <34.5 pg/mL: Sn 83.8%, Sp 97%	Cross-sectional study
Makwana 2020[2]	Women aged 25–75 years who had their last menstrual period >1 year back (n = 120)	Vaginal pH FSH	Unclear All patients were post-menopausal. McNemar test was used to analyze the convergence of the two methods for the diagnosis of menopause	FSH >40: Sn 85%	Cross-sectional study
Arslan 2003[3]	Healthy women who donated at least two blood samples at approximately 1 year interval (n = 60)	FSH	None FSH levels of pre- and post-menopausal women were compared	The reliability of a single log transformed FSH measurement as determined by intraclass correlation coefficient 0.70 (95% CI 0.55, 0.82)	Cross-sectional study
Heinrich 2006[4]	Women aged 35–60 years examined during NHANES 1999–2000 (n = 576)	FSH	None They compared the FSH levels of the reproductive, menopause transition and post-menopause group	Reproductive and menopause transition stages FSH 13 mIU/mL: Sn 67.4% (95% CI 50.0, 81.1), Sp 88.1% (95% CI 81.1, 92.8) Menopause transition and post menopause stages FSH 45 mIU/mL: Sn 73.6% (95% CI 60.1, 83.7), Sp 70.6% (95% CI 52.4, 84.0)	Cross-sectional study
Chester 2018[5]	Postmenopausal women aged 50–79 years recruited from 1993 to 1998 at 40 US clinical centers. n= 27, 347	Conjugated Equine Estrogen (CEE) or CEE + medroxy-	Placebo	Overall mortality Cardiovascular mortality Coronary Heart Disease Stroke	Randomized controlled trial

		progesterone acetate		DVT Pulmonary Embolism Invasive breast cancer	

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10.2. Characteristics of Included Studies on Screening for Chronic Kidney Disease

Study ID	Design	Population	Exposure	Comparator	Outcomes
Hoy 2003[1]	Controlled study with median follow-up of 40.7 months	n = 594 Australian Aborigines	ACR, perindopril	Historically-matched controls, Australian general population	Mortality, progression to renal failure
Atthobari 2006[2]	Double-blind RCT	n = 864 General population (Netherlands) 28–75 years	UAC, fosinopril + pravastatin	Placebo	CV events, Cost-effectiveness analysis
Hoerger 2010[3]	Cost-effectiveness model simulation	n = 577 General population (USA) 50–90 years	UAC, ACR	No screening	Cost-effectiveness analysis

ACR, albumin-creatinine ratio; *CV*, cardiovascular; *RCT*, randomized controlled trial; *UAC*, urine albumin concentration.

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10.3. Risk of Bias Table for Included Studies on Screening for Hyperuricemia.

Study ID	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participant and Personnel (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition bias)	Selective Outcome reporting (Reporting bias)	Overall	Comments
Kanbay 2011	L	U	H	H	L	U	H	Open label, no placebo, short follow-up period
Goicoechea 2015	L	U	L	L	H	U	L	Unequal number of patients who completed the study, small sample size
Tahergdham 2013	L	L	L	U	L	U	L	Short follow, small sample
Liu 2015	L	U	H	H	H	U	H	Open label, high loss to follow-up
Jalal 2017	L	U	L	L	L	U	L	
McMullan 2017	L	L	L	L	H	U	L	
Sircar 2015	L	L	L	U	H	U	L	Small sample, short follow-up
Mukri 2018	U	U	H	H	L	U	H	Open label
Kumura 2018	L	L	L	L	H	L	L	
Badve 2020	L	L	L	U	H	U	L	
Gaffo 2021	L	U	L	U	H	L	L	
Doria 2020	U	U	L	U	H	L	L	

H, high; *L*, low; *U*, unclear.

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10.4. Risk of Bias Table for Included Studies on Screening for Malnutrition.

	Certainty assessment							No. of Patients	
Study ID	No. of Studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Intervention	Comparator
Jayedi 2020[1]	50	cohort	serious [a]	serious [b]	serious [c]	serious [d]	all plausible residual confounding would reduce the demonstrated effect dose response gradient no publication bias	2,056,428 (WC)	none
c	31	cohort	serious [a]	serious [b]	serious [c]	serious [d]	all plausible residual confounding would reduce the demonstrated effect dose response gradient no publication bias	1,112,816 (WHR)	none
Sahakyan (2015)[3]	1	cohort	serious [a]	Consistency unknown (single study)	serious [c]	serious [e]		15,184 (WHR)	none
Jayedi 2022[2]	79	cohort	serious [a]	serious [b]	serious [f]	very serious [d]	all plausible residual confounding would reduce the demonstrated effect dose response gradient relatively large effect size very strong association publication bias strongly suspected	21,459,955 (WC)	none
Jayedi 2022[2]	182	cohort	serious [a]	serious [b]	serious [f]	serious [d]	all plausible residual confounding would	5,585,850 (BMI)	none

							reduce the demonstrated effect dose response gradient strong association publication bias strongly suspected		
	Certainty assessment							No. of Participants	
Study ID	No. of Studies	Study design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator
Tang 2020[5]	20	cohort and case-control type studies	serious [a]	not serious	serious [g]	serious [e]	none	13,835 (MUAC)	BMI

[a] Cohort study design or mostly observational studies. [b] Point estimates vary widely across studies; High heterogeneity. [c] Mostly studies from Western countries, few papers from Asia. [d] High heterogeneity. [e] Wide confidence interval. [f] Mostly from North America, Europe and Far East. [g] Setting or population included were those that would most likely use an established low MUAC cut-off, e.g., people living with human immunodeficiency virus and/or tuberculosis, low-resource and development settings, and individuals at-risk of undernutrition.
BMI, body mass index; *MUAC*, mid-upper arm circumference; *WC*, waist circumference; *WHR*, waist-hip ratio.

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PERIODIC HEALTH EXAMINATION TASK FORCE ON RENAL, METABOLIC, NUTRITION, AND ENDOCRINE DISORDERS 2022

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COI Administrative Officer:	Ivy Cruz

SUMMARY OF COI DECLARATIONS

Name	Affiliation	Summary of Declared Conflicts of Interest	Management
Elizabeth Paz-Pacheco, MD	University of the Philippines Manila	Advisory Committee, Sanofi Speaker's Bureau	D Financial COI Assignment of a co-chair who has no financial COI
Raymond Oliva, MD	University of the Philippines Manila	Director, Astellas Pharma	B Non-financial COI
Cecilia Santos-Acuin, MD	University of the Philippines Los Baños	Research Advisory Board, Zuellig Family Foundation Research on Philippine nutrition situation, World Bank Technical Advisor, Philippine Multisectoral Nutrition Project 4 Speaker, ILSI Southeast Asia Philippines Editorial Board, Food Ethics Journal Involved in Philippine Guidelines on Nutrition Practice Board, Philippine Association of Nutrition Adjunct Professor, Institute of Human Nutrition & Food, University of the Philippines Los Baños Senior Scientist Human Nutrition, International Rice Research Institute	B Non-financial COI
Rey Jaime Tan, MD	University of the Philippines–Philippine General Hospital	Clinical Associate Professor and Medical Specialist III, University of the Philippines–Philippine General Hospital President, Sagip Buhay Medical Foundation, Inc. Trialist, ACHIEVE Trial (trial on aldosterone for end-stage renal disease)	B Non-financial COI
Anna Angelica Macalalad-Josue, MD (technical coordinator)	Philippine College of Endocrinology, Diabetes, and Metabolism	Husband was employed as Head of Medical Affairs of AstraZeneca until 2019. AstraZeneca promotes anti-diabetes medications.	D Financial COI Re-assigned as evidence review expert

Ma. Czarlota Acelejado-Valdenor, MD	Antipolo Doctors Hospital, Philippine Society of Nephrology	Receives honoraria from Astra Zeneca, LRI Therapharma, ownership of stocks Pasig Doctors Medical Center, Metro Antipolo Hospital and Medical Center, Director of hemodialysis center	D Financial COI May need to pair with another ERE that is unconflicted or transfer her to another topic where she is not conflicted
Janika Adrienne Balane	University of the Philippines–Philippine General Hospital	No COI	A
Agnes Baston, MD	Philippine Medical Association	Received speaker's honoraria for scientific lectures of the following: (1) Astra Zeneca, Inc; (2) Cathay YSL; (3) Zuellig Philippines	May need to pair with another ERE that is unconflicted or transfer her to another topic where she is not conflicted
Rommel Bataclan, MD	University of the East–Ramon Magsaysay Memorial Medical Center, International Society of Nephrology	Postgraduate speaker on dialysis with honoraria from B Braun	D Financial COI May need to work on a question that does not have dialysis as treatment
Antonio Faltado, Jr., MD	Lipa Medix Medical Center, Philippine College of Endocrinology, Diabetes, and Metabolism	Gives lectures or speaks for Astra Zeneca, Boehringer Ingelheim, Sanofi, Novo Nordisk, Unilab, GX International, Getz Pharma, Servier, Otsuka	D Financial COI May need to pair with another ERE that is unconflicted or transfer him to another topic where he is not conflicted

Katrina Gomez-Chua, MD	Makati Medical Society, Philippine Society of Public Health Physicians	No COI	A
Anna Francesca Mulles, MD	University of the Philippines–Philippine General Hospital	No COI	A
Karl Jeffrey Murillo, MD	University of the Philippines–Philippine General Hospital	No COI	A
Sahra May Paragas, MD	St. Luke's Medical Center, Philippine College of Endocrinology, Diabetes, and Metabolism Diabetes Study Council	Consultant for RiteMed Phils; qualitative study on the experience of employees during the pandemic sponsored by Grupong Tamang Alaga under RiteMed Phils	D Financial COI May need to pair with another ERE that is unconflicted or transfer her to another topic where she is not conflicted
Chona Patalen	Department of Science and Technology–Food and Nutrition Research Institute	Development of nutrition practice guidelines for the management of overweight and obesity, FNRI Seminar Series (July 4-6, 2018), National Conference of Nutrition Action Officers (August 23, 2018)	B Non-financial COI
Rogelio Velasco, Jr., MD	Philippine Heart Center	No COI	A
Danilo Baldemor, MD	Philippine College of Physicians	Speaker for pharma companies (Sanofi, Novo Nordisk, Novartis, Abbott Nutrition) for diabetes drugs	C Financial COI Cannot vote on CQ nos. 3 to 6
Charmaine Duante, MD	Department of Science and Technology–	Publications on Nutrition, obesity, diabetes in relation to being chief Science research specialist of	B Non-financial COI

	Food and Nutrition Research Institute	DOST.	
Catherine Danielle Duque-Lee, MD	Philippine Academy of Family Physicians	Regional Manager, Novo Nordisk Educational grant from Merck Foundation	C Financial COI Cannot vote on CQ no. 3
Marimel Lamsin	Philippine Alliance of Patient Organizations	No COI	A
Emelita Lavilla, RND, MHA	Philippine Association of Nutrition	Lectures on obesity and diabetes to nurses and interns	B Non-financial COI
Vimar Luz, MD	Philippine Society of Nephrology	Medical director of dialysis centers	C Financial COI Cannot vote on CQ no. 4
Daveric Pagsisihan, MD	Philippine College of Endocrinology, Diabetes, and Metabolism	Speaker for anti-diabetes, antihypertensive and anti-thyroid drugs	C Financial COI Cannot vote on CQ nos. 2 and 3
Olive Quizon, MD	Philippine Academy of Family Physicians	Medical affairs officer of Abbott, speaker's bureau for different pharma companies	C Financial COI Cannot vote on CQ nos. 5 and 6s
Maria Theresa Talavera, RND, DrPH	Philippine Association of Nutrition	Research and publications on obesity and acute malnutrition funded by UNICEF	B Non-financial COI
Jeanne Tiangha-Gonzales, MD	Association of Municipal Health Officers of the Philippines	No COI	A

SEARCH STRATEGY

Serum Follicle-stimulating Hormone, Luteinizing Hormone, and Estradiol in Screening for High Climacteric Syndrome

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Pubmed	(menopause[MeSH Terms]) AND (philippines[MeSH Terms])	Nov. 13, 2022 1:00PM	29	2
Pubmed	(Climacteric syndrome[MeSH Terms]) AND (Screening[MeSH Terms])	Nov 13, 2022 1:15PM	1	0
Google scholar	Screening of climacteric syndrome, 2017-2022	Nov 13, 2022 2:00PM	1,680	5
Google scholar	Climacteric, Filipino	Nov 13, 2022 5:00PM	3	3
Pubmed	((Climacteric[MeSH Terms]) AND (Screening[MeSH Terms])) AND (vasomotor symptoms[MeSH Terms])	Nov 14, 2022 8:00AM	7	1
Pubmed	((climacteric[MeSH Terms]) AND (syndrome[MeSH Terms])) AND (symptoms[MeSH Terms])	Nov 14, 2022 8:20AM	142	4
Pubmed	(screening[MeSH Terms]) AND (climacteric syndrome[MeSH Terms])	Nov 14, 2022 9:10AM	1	0
Pubmed	((Screening[MeSH Terms]) AND (menopause[MeSH Terms])) AND (follicle-stimulating hormone[MeSH Terms])	Nov 16, 2022 1:00PM	2	0
Pubmed	((menopause[MeSH Terms]) AND (screening[MeSH Terms])) AND (luteinizing hormone[MeSH Terms])	Nov 16, 2022 1:20PM	0	0
Pubmed	((menopause[MeSH Terms]) AND (screening[MeSH Terms])) AND (estradiol[MeSH Terms])	Nov 30, 2022 9:05AM	7	0
Clinical cardiology	Menopause hormone therapy and cardiovascular disease	Nov 30, 2022 10:10AM	46	1
JAMA Network	Hormone Replacement Therapy, Menopause, Randomized Controlled Trial	Dec 1, 2022 7:05PM	21	3
Pubmed	((screening[MeSH terms]) AND follicle stimulating hormone [MeSH Terms])) AND (menopause [MeSH Terms])	Dec 1, 2022 8:20PM	2	0
Pubmed	(((benefits[MeSH Terms]) AND (harms[MeSH Terms])) AND (menopausal hormone therapy[MeSH Terms])) AND (cardiovascular disease[MeSH Terms])	Dec 1, 2022 9:20PM	0	0
Biomed central	FSH and menopause	Dec 5, 2022 8:10AM	26	2

Serum Calcium, Electrocardiogram, and Bone Mineral Density in Screening for Hypocalcemia or Hypercalcemia

	Query	Filters	Search Details	Results
40	#1 AND #29 AND #39		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]) AND ("Bone Density"[MeSH Terms] OR "bone mineral density test"[All Fields] OR "BMD test"[All Fields] OR "bone densitometry"[All Fields])	147
41	#2 AND #29 AND #39		("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]) AND ("Bone Density"[MeSH Terms] OR "bone mineral density test"[All Fields] OR "BMD test"[All Fields] OR "bone densitometry"[All Fields])	83
39	"Bone Density"[Mesh] OR "bone mineral density test" OR "BMD test" OR "bone densitometry"		"Bone Density"[MeSH Terms] OR "bone mineral density test"[All Fields] OR "BMD test"[All Fields] OR "bone densitometry"[All Fields]	61,586
35	#2 AND #29 AND #21		("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]) AND ("calcium/blood"[MeSH Terms] OR "serum calcium"[All Fields] OR "corrected calcium"[All Fields])	1,204
34	#2 AND #29 AND #21	Clinical Trial, Meta-Analysis, Randomized Controlled Trial	(("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]) AND ("calcium/blood"[MeSH Terms] OR "serum calcium"[All Fields] OR "corrected calcium"[All Fields])) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter])	58
33	#1 AND #29 AND #21	Clinical Trial, Meta-Analysis, Randomized Controlled Trial	(("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]) AND ("calcium/blood"[MeSH Terms] OR "serum calcium"[All Fields] OR "corrected calcium"[All Fields])) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter])	45
30	#1 AND #29 AND #21		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]) AND ("calcium/blood"[MeSH Terms] OR "serum calcium"[All Fields] OR "corrected calcium"[All Fields])	2,121
29	#3 OR diagnos*		"screening"[All Fields] OR "mass screening"[MeSH Terms] OR "diagnos*"[All Fields]	6,544,049
28	#1 AND #3 AND #21		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms]) AND ("calcium/blood"[MeSH Terms] OR "serum calcium"[All Fields] OR "corrected calcium"[All Fields])	146
21	"calcium/blood"[MeSH] OR "serum calcium" OR "corrected calcium"		"calcium/blood"[MeSH Terms] OR "serum calcium"[All Fields] OR "corrected calcium"[All Fields]	39,999
20	#2 AND #3 AND #16		("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms]) AND ("electrocardiogram"[All Fields] OR "ECG"[All Fields] OR "12 lead electrocardiogram"[All Fields] OR "12L ECG"[All Fields] OR "Electrocardiography"[MeSH Terms])	11
19	#2 AND #16		("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("electrocardiogram"[All Fields] OR "ECG"[All Fields] OR "12 lead electrocardiogram"[All Fields] OR "12L ECG"[All Fields] OR "Electrocardiography"[MeSH Terms])	444

18	#1 AND #3 AND #16		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms]) AND ("electrocardiogram"[All Fields] OR "ECG"[All Fields] OR "12 lead electrocardiogram"[All Fields] OR "12L ECG"[All Fields] OR "Electrocardiography"[MeSH Terms])	6
17	#1 AND #16		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("electrocardiogram"[All Fields] OR "ECG"[All Fields] OR "12 lead electrocardiogram"[All Fields] OR "12L ECG"[All Fields] OR "Electrocardiography"[MeSH Terms])	249
16	"electrocardiogram" OR "ECG" OR "12 lead electrocardiogram" OR "12L ECG" OR "Electrocardiography"[Mesh]		"electrocardiogram"[All Fields] OR "ECG"[All Fields] OR "12 lead electrocardiogram"[All Fields] OR "12L ECG"[All Fields] OR "Electrocardiography"[MeSH Terms]	259,498
15	"electrocardiogram" OR "ECG" OR "12 lead electrocardiogram" OR "12L ECG"		"electrocardiogram"[All Fields] OR "ECG"[All Fields] OR "12 lead electrocardiogram"[All Fields] OR "12L ECG"[All Fields]	104,303
14	#2 AND #3	Clinical Trial, Meta-Analysis, Randomized Controlled Trial	(("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms])) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter])	13
10	#2 AND #3 AND #4		("Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms]) AND ("healthy adults"[All Fields] OR "asymptomatic adults"[All Fields])	1
9	#1 AND #3	Meta-Analysis, Randomized Controlled Trial, Systematic Review	(("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms])) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])	13
6	#1 AND #3		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms])	385
5	#1 AND #3 AND #4		("Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]) AND ("screening"[All Fields] OR "mass screening"[MeSH Terms]) AND ("healthy adults"[All Fields] OR "asymptomatic adults"[All Fields])	3
4	"healthy adults" OR "asymptomatic adults"		"healthy adults"[All Fields] OR "asymptomatic adults"[All Fields]	31,069
3	"screening" OR "mass screening"[MeSH Terms]		"screening"[All Fields] OR "mass screening"[MeSH Terms]	771,926
2	"Hypocalcemia"[All Fields] OR "hypocalcemia"[MeSH Terms]		"Hypocalcemia"[All Fields] OR "Hypocalcemia"[MeSH Terms]	15,983
1	"Hypercalcemia"[All Fields] OR "hypercalcemia"[MeSH Terms]		"Hypercalcemia"[All Fields] OR "Hypercalcemia"[MeSH Terms]	21,243

	Query	**Filters**	**Search Details**	**Results**

17	#1 AND #12 AND (#6 OR #7 OR #8 OR #9)		("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND ("alendronate"[MeSH Terms] OR "alendronate"[All Fields] OR "alendronate s"[All Fields] OR "alendronates"[All Fields] OR "alendronic"[All Fields] OR ("risedronate s"[All Fields] OR "risedronic acid"[MeSH Terms] OR ("risedronic"[All Fields] AND "acid"[All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields] OR "risedronic"[All Fields]) OR ("pamidronate"[MeSH Terms] OR "pamidronate"[All Fields] OR "pamidronic"[All Fields]) OR "zoledron*"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields]) OR "fracture*"[All Fields] OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) OR "CV"[All Fields]))	6
16	#1 AND #12 AND (#6 OR #7 OR #8 OR #9)	Clinical Trial, Meta-Analysis	(("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND ("alendronate"[MeSH Terms] OR "alendronate"[All Fields] OR "alendronate s"[All Fields] OR "alendronates"[All Fields] OR "alendronic"[All Fields] OR ("risedronate s"[All Fields] OR "risedronic acid"[MeSH Terms] OR ("risedronic"[All Fields] AND "acid"[All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields] OR "risedronic"[All Fields]) OR ("pamidronate"[MeSH Terms] OR "pamidronate"[All Fields] OR "pamidronic"[All Fields]) OR "zoledron*"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields]) OR "fracture*"[All Fields] OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) OR "CV"[All Fields]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter])	1
15	#1 AND #12	Clinical Trial, Meta-Analysis	(("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND ("alendronate"[MeSH Terms] OR "alendronate"[All Fields] OR "alendronate s"[All Fields] OR "alendronates"[All Fields] OR "alendronic"[All Fields] OR ("risedronate s"[All Fields] OR "risedronic acid"[MeSH Terms] OR ("risedronic"[All Fields] AND "acid"[All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields] OR "risedronic"[All Fields]) OR ("pamidronate"[MeSH Terms] OR "pamidronate"[All Fields] OR "pamidronic"[All Fields]) OR "zoledron*"[All Fields])) AND (clinicaltrial[Filter] OR meta-analysis[Filter])	6

14	#1 AND #12	Meta-Analysis	(("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND ("alendronate"[MeSH Terms] OR "alendronate"[All Fields] OR "alendronate s"[All Fields] OR "alendronates"[All Fields] OR "alendronic"[All Fields] OR ("risedronate s"[All Fields] OR "risedronic acid"[MeSH Terms] OR ("risedronic"[All Fields] AND "acid"[All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields] OR "risedronic"[All Fields]) OR ("pamidronate"[MeSH Terms] OR "pamidronate"[All Fields] OR "pamidronic"[All Fields]) OR "zoledron*"[All Fields])) AND (meta-analysis[Filter])	2
13	#1 AND #12		("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND ("alendronate"[MeSH Terms] OR "alendronate"[All Fields] OR "alendronate s"[All Fields] OR "alendronates"[All Fields] OR "alendronic"[All Fields] OR ("risedronate s"[All Fields] OR "risedronic acid"[MeSH Terms] OR ("risedronic"[All Fields] AND "acid"[All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields] OR "risedronic"[All Fields]) OR ("pamidronate"[MeSH Terms] OR "pamidronate"[All Fields] OR "pamidronic"[All Fields]) OR "zoledron*"[All Fields])	21
12	alendronate OR risedronate OR pamidronate OR zoledron*		"alendronate"[MeSH Terms] OR "alendronate"[All Fields] OR "alendronate s"[All Fields] OR "alendronates"[All Fields] OR "alendronic"[All Fields] OR ("risedronate s"[All Fields] OR "risedronic acid"[MeSH Terms] OR ("risedronic"[All Fields] AND "acid"[All Fields]) OR "risedronic acid"[All Fields] OR "risedronate"[All Fields] OR "risedronic"[All Fields]) OR ("pamidronate"[MeSH Terms] OR "pamidronate"[All Fields] OR "pamidronic"[All Fields]) OR "zoledron*"[All Fields]	15,209
10	#1 AND #2 AND (#6 OR #7 OR #8 OR #9)		("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND "parathyroidectomy"[All Fields] AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields]) OR "fracture*"[All Fields] OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) OR "CV"[All Fields]))	199
11	#1 AND #2 AND (#6 OR #7 OR #8 OR #9)	Meta-Analysis	(("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND "parathyroidectomy"[All Fields] AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ("epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All	2

			Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields]) OR "fracture*"[All Fields] OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) OR "CV"[All Fields])) AND (meta-analysis[Filter])	
9	cardiovascular OR cardiac OR CV		"cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) OR "CV"[All Fields]	3,240,421
8	fracture*		"fracture*"[All Fields]	357,678
7	morbidity		"epidemiology"[MeSH Subheading] OR "epidemiology"[All Fields] OR "morbidity"[All Fields] OR "morbidity"[MeSH Terms] OR "morbid"[All Fields] OR "morbidities"[All Fields] OR "morbids"[All Fields]	3,450,811
6	mortality		"mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading]	1,519,227
4	#1 AND #2	Meta-Analysis	(("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND "parathyroidectomy"[All Fields]) AND (meta-analysis[Filter])	4
3	#1 AND #2		("asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))) AND "parathyroidectomy"[All Fields]	485
2	"parathyroidectomy"		"parathyroidectomy"[All Fields]	9,590
1	"asymptomatic hyperparathyroidism" OR "mild hyperparathyroidism" OR asymptomatic primary hyperparathyroidism		"asymptomatic hyperparathyroidism"[All Fields] OR "mild hyperparathyroidism"[All Fields] OR (("asymptomatic"[All Fields] OR "asymptomatically"[All Fields] OR "asymptomatics"[All Fields]) AND ("hyperparathyroidism, primary"[MeSH Terms] OR ("hyperparathyroidism"[All Fields] AND "primary"[All Fields]) OR "primary hyperparathyroidism"[All Fields] OR ("primary"[All Fields] AND "hyperparathyroidism"[All Fields])))	1,141

Fasting Plasma Glucose and Hemoglobin A_{1C} in Screening for Prediabetes or Type 2 Diabetes Mellitus

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible

Medline	**((((prediabetes) OR (impaired fasting glucose)) OR (impaired glucose tolerance)) AND (screening)) AND (general population)**	Nov. 21, 2022 8:00PM	106232 abstracts retrieved	0
CENTRAL	#1 Screening for prediabetes #2 Screening for impaired glucose tolerance #3Screening for impaired fasting glucose #4 HbA1c #5 Fasting plasma glucose #6 Oral glucose tolerance test #7 General population, asymptomatic adults #8 #1 OR #2 OR # 3 #9 # 4 OR #5 OR #6 #10 #8 AND #9 AND #7	Nov. 21, 2022 8:30PM	19	0

Estimated Glomerular Filtration Rate, Urine Albumin-creatinine Ratio, Urine Albumin Concentration, and Kidney Ultrasonography in Screening for Chronic Kidney Disease

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	chronic kidney disease AND screening AND albuminuria AND general population in All Text - in Cochrane Reviews, Cochrane Protocols, Trials (Word variations have been searched)	August 28, 2021 11:00AM	63	4
Cochrane	chronic kidney disease [Mesh] AND screening AND proteinuria AND general population in All Text - in Cochrane Reviews, Cochrane Protocols, Trials (Word variations have been searched)	January 2023	113	2
Google Scholar	chronic kidney disease [Mesh] AND screening AND proteinuria AND general population in All Text - (Word variations have been searched)	January 2023	40	0

Serum Uric Acid in Screening for Hyperuricemia

Search	Query	Results	Time
#7	Search: **#1 AND #2** Filters: **Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Systematic Review**	227	07:54:50
#6	Search: **#1 AND #2** Filters: **Clinical Trial, Meta-Analysis, Randomized Controlled Trial**	210	07:51:57
#5	Search: **#1 AND #2** Filters: **Clinical Trial, Randomized Controlled Trial**	167	07:51:49
#4	Search: **#1 AND #2** Filters: **Clinical Trial**	167	07:51:42
#3	Search: **#1 AND #2**	1,274	07:51:32
#2	Search: **((((((hyperuricemia[MeSH Terms]) OR (elevated uric acid[MeSH Terms])) OR (high uric acid[MeSH Terms])) OR (elevated serum uric acid)) OR (high serum uric acid))) OR (asymptomatic hyperuricemi*)**	13,621	07:51:23

Search	Query	Results	Time
#1	Search: **(febuxostat[Title/Abstract]) OR (allopurinol[Title/Abstract])**	8,158	07:51:14

Anthropometric Measurements in Screening for Malnutrition

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
PubMed	(Adults OR Adult OR Men OR Women) (Obesity OR Adiposity OR “central fatness” OR overweight OR “body mass index” OR “BMI” “waist circumference” OR "hip circumference” OR “waist-hip ratio” OR “waist-to-hip ratio” OR “anthropometric measurements”) (“all-cause mortality” OR “cardiovascular mortality”) (“systematic review”) Filters: January 1, 2020 to March 4, 2023	February 19, 2023 7:39PM	449 26	 1
PubMed	(Adults OR Adult OR Men OR Women) (Obesity OR Adiposity OR “central fatness” OR overweight OR “body mass index” OR “BMI” “waist circumference” OR "hip circumference” OR “waist-hip ratio” OR “waist-to-hip ratio OR “anthropometric measurements”) (diabetes OR “Diabetes Mellitus”) Filters: January 1, 2020 to March 4, 2023	February 20, 2023 10:34AM	2184	2
PubMed	(Adults OR Adult OR Men OR Women) (“mid-upper arm circumference” OR “arm circumference” OR MUAC) (“systematic review”) Filters: January 1, 2020 to March 4, 2023	January 27, 2023 3:13PM	440	1
Hand-search	(Adults OR Adult OR Men OR Women) (Obesity OR Adiposity OR “central fatness” OR overweight OR “body mass index” OR “BMI” “waist circumference” OR "hip circumference” OR “waist-hip ratio” OR “waist-to-hip ratio OR “anthropometric measurements”) (diabetes OR “Diabetes Mellitus”)	March 5, 2023		1

Hemoglobin and Red Blood Cell Parameters in Screening for Nutritional Anemia

Database	Search Strategy / Search Terms	Date and Time off Search	Results	
			Yield	Eligible
Medline	Anemia screening OR nutritional anemia OR hemoglobin screening OR RBC indices OR MCV and MCH. Filters: January 2017 to January 13, 2023	January 13, 2023 11:00 am	1162	6
Cochrane Library	Anemia screening OR nutritional anemia OR hemoglobin screening OR RBC indices OR MCV and MCH. Filters: January 2017 to January 13, 2023	January 13, 2023 1:00pm	0	0
Google Scholar	Anemia screening OR nutritional anemia OR hemoglobin screening OR RBC indices OR MCV and MCH. Filters: January 2017 to January 13, 2023	January 13, 2023 2:00 pm	11	0

Tanner Staging in Screening for Differences in Timing of Sexual Maturity

Database	Search Strategy / Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Pubmed.gov	((("tanner"[All Fields] OR "tanner s"[All Fields] OR "tanners"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields])) OR (("sexual behavior"[MeSH Terms] OR ("sexual"[All Fields] AND "behavior"[All Fields]) OR "sexual behavior"[All Fields] OR "sexual"[All Fields] OR "sexually"[All Fields] OR "sexualities"[All Fields] OR "sexuality"[MeSH Terms] OR "sexuality"[All Fields] OR "sexualization"[All Fields] OR "sexualize"[All Fields] OR "sexualized"[All Fields] OR "sexualizing"[All Fields] OR "sexuals"[All Fields]) AND ("maturate"[All Fields] OR "maturated"[All Fields] OR "maturating"[All Fields] OR "maturation"[All Fields] OR "maturational"[All Fields] OR "maturations"[All Fields] OR "maturative"[All Fields] OR "mature"[All Fields] OR "matured"[All Fields] OR "maturer"[All Fields] OR "maturers"[All Fields] OR "matures"[All Fields] OR "maturing"[All Fields] OR "maturities"[All Fields] OR "maturity"[All Fields]) AND ("rated"[All Fields] OR "ratee"[All Fields] OR "ratees"[All Fields] OR "rating"[All Fields] OR "ratings"[All Fields]))) AND ("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields] OR "quality of life"[MeSH Terms] OR "QoL"[All Fields])	8 February 2023 1900H	63	2
Cochrane Library	Tanner Staging and Quality of Life Limitations: Studies from 2019	8 February 2023	0	0

AGREE REPORTING CHECKLIST (SELF EVALUATION)

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☒ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	18, 19
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	13–15
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☒ Excluded populations (if relevant)	17, 18
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☒ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	85, 86
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) ☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	23
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	2
DOMAIN 3: RIGOUR OF DEVELOPMENT		

7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	20, 91–99
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☐ Language (if relevant) ☐ Context (if relevant)	79–84
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the studies. Tools exist that can facilitate the reporting of this concept.*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered ☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	25–27, 32, 33, 36–38, 41, 42, 46, 47, 51–54, 58–60, 62–64
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	20–23
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☒ Supporting data and report of benefits ☒ Supporting data and reqport of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	25–27, 32, 33, 36–38, 41, 42, 46, 47, 51–54, 58–60, 62–64

12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	23, 30, 35, 40, 45, 49, 57, 62
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence) ☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☐ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	22
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☐ Methodology for the updating procedure	12
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	23, 30, 35, 40, 45, 49, 57, 62
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	23–25, 30–32, 35, 36, 40, 41,

		45, 46, 49–51, 57, 58, 62
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	13–15, 23, 30, 35, 40, 45, 49, 57, 62
DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☒ How the information influenced the guideline development process and/or formation of the recommendations	21, 22
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals o Solutions linked to barrier analysis (see Item 18) o Tools to capitalize on guideline facilitators (see Item 18) o Outcome of pilot test and lessons learned	3
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry	27, 28, 33, 38, 42, 43, 47, 54, 60, 64

	(e.g., specific drug acquisition costs per treatment course) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☐ Advice on the frequency and interval of measurement ☐ Operational definitions of how the criteria should be measured	22, 65-66
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☐ A statement that the funding body did not influence the content of the guideline	20
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	87–90