

**UNIVERSIDAD PERUANA UNIÓN**

FACULTAD DE CIENCIAS DE LA SALUD

Escuela Profesional de Medicina Humana



*Una Institución Adventista*

**Copeptin and metabolic syndrome: a systematic review**

Tesis para obtener el Título Profesional de Médico Cirujano

**Autor:**

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Lima, abril del 2022

# DECLARACIÓN JURADA DE AUTORÍA DE TESIS

Brenda Mireya Galindo Yllu, de la Facultad de Ciencias de la Salud, Escuela Profesional de Medicina Humana, de la Universidad Peruana Unión.

DECLARO:

Que la presente investigación titulada: **“Copeptin and metabolic syndrome: a systematic review”** constituye la memoria que presenta la Bachiller Brenda Mireya Galindo Yllu para obtener el título de Profesional de Medicina Humana, cuya tesis ha sido realizada en la Universidad Peruana Unión bajo mi dirección.

Las opiniones y declaraciones en este informe son de entera responsabilidad del autor, sin comprometer a la institución.

Y estando de acuerdo, firmo la presente declaración en la ciudad de Lima, a los 27 días del mes de abril del año 2022.



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Salomon Huancahuire Vega

## ACTA DE SUSTENTACIÓN DE TESIS

En Lima, Naña, Villa Unión, a 06 día(s) del mes de abril del año 2022, siendo las 20:00 horas, se reunieron los miembros del jurado en la Universidad Peruana Unión Campus Lima, bajo la dirección del (de la) presidente(a).

Mg. Pool Marcos Corbojal el (la) secretario(a): Mg. Manuel David Concha Toledo y los demás miembros: Mtro. Luis Felipe Segura Chávez y el (la) asesor(a) Dr. Salomón Huancachire Vega con el propósito de administrar el acto académico de sustentación de la tesis titulado:

Copeptin and metabolic syndrome: a systematic review

del(los) bachiller(es): a) Brenda Mireya Galindo Yllu

b)

c)

conducente a la obtención del título profesional de:

Médico Cirujano  
(Denominación del Título Profesional)

El Presidente inició el acto académico de sustentación invitando al (a la) / a (los) (las) candidato(a)/s hacer uso del tiempo determinado para su exposición. Concluida la exposición, el Presidente invitó a los demás miembros del jurado a efectuar las preguntas, y aclaraciones pertinentes, las cuales fueron absueltas por al (a la) / a (los) (las) candidato(a)/s. Luego, se produjo un receso para las deliberaciones y la emisión del dictamen del jurado.

Posteriormente, el jurado procedió a dejar constancia escrita sobre la evaluación en la presente acta, con el dictamen siguiente:

Bachiller (a): Brenda Mireya Galindo Yllu

| CALIFICACIÓN    | ESCALAS   |           |              | Mérito           |
|-----------------|-----------|-----------|--------------|------------------|
|                 | Vigesimal | Literal   | Cualitativa  |                  |
| <u>Aprobado</u> | <u>15</u> | <u>B-</u> | <u>Bueno</u> | <u>Muy bueno</u> |

Bachiller (b):

| CALIFICACIÓN | ESCALAS   |         |             | Mérito |
|--------------|-----------|---------|-------------|--------|
|              | Vigesimal | Literal | Cualitativa |        |
|              |           |         |             |        |

Bachiller (c):

| CALIFICACIÓN | ESCALAS   |         |             | Mérito |
|--------------|-----------|---------|-------------|--------|
|              | Vigesimal | Literal | Cualitativa |        |
|              |           |         |             |        |

(\*) Ver parte posterior

Finalmente, el Presidente del jurado invitó al (a la) / a (los) (las) candidato(a)/s a ponerse de pie, para recibir la evaluación final y concluir el acto académico de sustentación procediéndose a registrar las firmas respectivas.

\_\_\_\_\_  
Presidente/a

[Firma]  
Secretario/a

\_\_\_\_\_  
Asesor/a

\_\_\_\_\_  
Miembro

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Miembro

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Bachiller (a)

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Bachiller (b)

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Bachiller (c)

## **Agradecimientos y dedicatoria**

Lo dedico a Dios, a mis padres Luis Enrique Galindo Bendezu y Mireya Zully Yllu Soto y a mi familia. Agradezco a los doctores Jessica Hanae Zafra Tanaka, Salomon Huanchuire Vega y compañeros Ricardo Rojas Humpire y Renato Soriano Moreno por su apoyo durante el proceso del trabajo y sumisión a la revista para publicación y contribución con el conocimiento.

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## **Abstract**

**Background:** Copeptin, a reliable marker for vasopressin release, has been associated with cardiometabolic diseases including metabolic syndrome (MetS). This systematic review aims to evaluate the association between copeptin and MetS.

**Methods:** We searched in Pubmed, Scopus, EMBASE, and Web of Science databases until March 2021 and included observational studies (cohort studies, cross-sectional, and case-control) reporting the risk or prevalence of having MetS in patients with elevated copeptin levels compared to patients without elevated copeptin levels. Risk of bias was evaluated with the New Castle-Ottawa Scale. Meta-analysis was not performed because of the heterogeneity of the copeptin cut-off values.

**Results:** A total of 7 studies (5 cross-sectional, 1 case-control, 1 cohort) were included comprising 11 699 participants. Most of them were performed in the adult general population. Two cross-sectional and the case-control studies found a positive significant association between higher levels of copeptin and the MetS. While three cross-sectional and the cohort study found no association. The case-control study had several methodological limitations, most cross-sectional studies were methodologically adequate and the cohort study had no methodological issues.

**Conclusions:** The association between copeptin and MetS is inconsistent. However, this biomarker could be important for the early detection of MetS and implementation of preventive interventions. Thus, future studies should corroborate this association.

**Keywords:** Copeptin, metabolic syndrome, biomarker, systematic review.

## **Introduction**

Metabolic syndrome (MetS) is a set of interrelated disorders characterized by hypertension, hyperglycemia, obesity, and insulin resistance (1). This pathologic condition is very common around the world, the estimated worldwide prevalence is 25%, approximately three times more frequent than type 2 diabetes mellitus (T2DM). However, the frequency and distribution of MetS vary according to the diagnostic criteria applied, race, culture, and geographic location (2–4).

The impact of MetS is evident as a risk factor for T2DM, atheroma plaque formation, acute myocardial infarction, cerebrovascular disease, and other cardiovascular events, through progressive endothelial damage and inflammatory cellular microenvironment (2,5–7). Therefore, it is important to detect in its early stages and manage cases of MetS to avoid the development of complications.

There are several international criteria to diagnose MetS, but progress in metabolic research reveals that the environment where MetS develops is more complex than previously thought. In this regard, the interactions of endocrine and paracrine secretory products in key tissues of metabolic control are affected (4,8). Some of these metabolites, such as cytokines, miRNA, microvesicles/exosomes, and components of the renin-angiotensin-aldosterone system, are of particular interest as biomarkers and drug targets in MetS (9–11).

In recent years, the C-terminal sequence of pre-pro vasopressin (Copeptin), a 39-amino acid-long glycosylated peptide secreted equimolarly with arginine-vasopressin (AVP), has been used as an alternative marker of AVP because of its long-term stability and being easy to measure on blood (12,13). Copeptin is related to several cardiometabolic disorders, such as heart failure, T2DM, polycystic ovary syndrome, preeclampsia, and renal disease (14–19). This is attributed to the overstimulation of vasopressin receptors (rV) located in different tissues involved in metabolic control (20). In this sense, animal studies show that the convergence in rV1a and rV1b stimuli generates insulin resistance and hyperglycemia, caused by excessive activation of  $\beta$ -oxidation and adrenocorticotrophic hormone release. While, the coordinate activation of rV1a, rV1b, and rV2, adds water and sodium retention that induces the development of hypertension (21). Copeptin

might play an important role in MetS physiopathology and could potentially be used as an early biomarker, however, there is not enough evidence about the association between copeptin and MetS. Thus, we aim to determine the relationship between serum copeptin levels and their association with MetS in human populations, because of its importance as a possible early biomarker of cardiovascular disorders related to MetS.

## **Methods**

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines 2021 (22). The study protocol is registered in PROSPERO (CRD42021236587).

### **Study selection**

We included original cohort, cross-sectional and case-control studies that reported the following effect measures: the risk ratio, odds ratio, hazard ratio, prevalence ratio, or data that allows estimation of any of the above-mentioned effect measures contrasting the risk of having MetS in patients with elevated copeptin levels compared to patients without elevated copeptin levels, as defined by the individual studies. Studies reporting any diagnostic criteria for MetS (National Cholesterol Education Program - ATP III, International Diabetes Federation, American Heart Association/National Heart, Lung, and Blood Institute, and others) were included. On the other hand, we excluded case reports, editorials, commentaries, clinical practice guidelines, opinions, reviews, systematic reviews studies, and studies for which full text was not available. There were no restrictions on language or publication date.

### **Literature search**

We searched articles in four databases: 1) PubMed, 2) Web of Science, 3) Scopus, and 4) EMBASE until March 2021 (see **Supplementary Material 1**). Duplicated records were manually removed using the Rayyan software (23), and two review authors (BGY and RRH) independently screened the results to identify potentially relevant studies for inclusion (first reading the titles and abstracts, and after that reading the full text of the articles). Any disagreement on selection

was discussed with a third party (DRSM) and resolved by consensus. After that, we complemented the search by reviewing the lists of references of all included studies. If a full-text was not available, we sent an email to the author to request the article.

## Supplementary material 1. Search strategy

| Database | Search strategy   |
|----------|---|
| Pubmed   | #1 Metabolic syndrome<br>"Metabolic Syndrome"[Mesh] OR "Metabolic Syndrom*"[tiab] OR "Insulin Resistance Syndrome"[tiab] OR "Dysmetabolic Syndrome X"[tiab] OR "Reaven Syndrome X"[tiab] OR "Metabolic Cardiovascular Syndrome"[tiab] OR "Cardiometabolic Syndrom*"[tiab] OR "Metabolic Syndrom*"[OT] OR "Insulin Resistance Syndrome" [OT] OR "Dysmetabolic Syndrome X"[OT] OR "Reaven Syndrome X" [OT] OR "Metabolic Cardiovascular Syndrome" [OT] OR "Cardiometabolic Syndrom*"[OT]<br>#2 Copeptin<br>Copeptins [Supplementary Concept] OR Copeptin* [TIAB] OR ((C-terminal [TIAB] OR "C terminal" [TIAB]) AND (AVP [TIAB] OR vasopressin [TIAB] OR proargipressin [TIAB] OR provasopressin [TIAB])) OR Copeptin* [OT] OR ((C-terminal [OT] OR "C terminal" [OT]) AND (AVP [OT] OR vasopressin [OT] OR proargipressin [OT] OR provasopressin [OT]))<br>(#1 AND #2) |
| Scopus   | TITLE-ABS-KEY("Insulin Resistance Syndrome" OR "Reaven Syndrome X") OR TITLE-ABS-KEY (*metabolic W/2 Syndrom*)<br>TITLE-ABS-KEY(Copeptin* OR ((C-terminal OR "C terminal") W/3 (AVP OR vasopressin OR proargipressin OR provasopressin)))<br>(#1 AND #2)  |
| WOS      | TS=("Insulin Resistance Syndrome" OR "Reaven Syndrome X") OR TS=(*metabolic NEAR/2 Syndrom*)<br>TS=(Copeptin* OR ((C-terminal OR "C terminal") NEAR/3 (AVP OR vasopressin OR proargipressin OR provasopressin)))<br>(#1 AND #2)   |
| Embase   | 'metabolic syndrome X'/exp OR ('Insulin Resistance Syndrome' OR 'Reaven Syndrome X'):ti,ab,kw OR ((metabolic OR dysmetabolic OR cardiometabolic) NEAR/2 Syndrom*):ti,ab,kw<br>Copeptin/exp OR (Copeptin* OR ((C-terminal OR 'C terminal') NEAR/3 (AVP OR vasopressin OR proargipressin OR provasopressin))):ti,ab,kw<br>(#1 AND #2)   |

### Data extraction

Two independent authors (BGY and RRH) independently performed data extraction from each included study using a standardized Microsoft Excel sheet, with any differences resolved by a third researcher (DRSM).

The following variables were extracted from each study: first author, year of publication, country, study design, population characteristics (number of participants, age, sex), copeptin measurement, copeptin values, MetS diagnostic criteria, MetS prevalence, cut-off points of copeptin values and the effect measures of the relationship between copeptin and MetS. When there were doubts about any information reported in the studies, we sent an email to the authors to clarify the information.

## **Risk of bias**

We assessed the risk of bias of the included studies using the New Castle-Ottawa Scale (NOS) (24). To homogenize the assessments, we held training on the use of the tool and used a list of criteria to assess each of the NOS questions. The NOS has specific versions according to study design (cross-sectional, cohort, and case-control) and consists of three domains: selection, comparability, and outcome/exposure. The maximum score for cross-sectional studies is 10, while for cohort and case-control studies is 9. Two researchers (BGY and RRH) carried out this process independently. In case of disagreement, a consensus was achieved with a third researcher (DRSM and JHZZ).

## **Statistical analyses**

We present a description of the included studies and their results. We decided not to conduct meta-analyses because of the heterogeneity between the studies; different study designs, diagnostic criteria for MetS, and cut-off points for copeptin values.

## **Results**

### **Studies characteristics**

In the database systematic search, we identified 84 records after removing duplicates. From these, we reviewed 26 full-text for eligibility, and finally, 7 studies were included (**Supplementary Material 2**). No new article was identified by reviewing the references of all included studies. (**Figure 1**).

The characteristics of the 7 studies are summarized in **Table 1**. The number of participants ranged from 80 to 4742. Five studies were cross-sectional, one cohort, and one case-control. Enhörning - 2011 (25) and Enhörning – 2013 (26) share part of the population but have different study designs. Regarding the population, Saleem - 2009 (27) evaluated adult African Americans (mean age 63.6) and non-Hispanic Whites (mean age 58.9), and Deligözoğlu - 2020 (28) included obese children, who were between 10 and 18 years of age. The rest of the studies were performed in general adult community populations with mean ages ranging from 47.4 to 57.5 (29–31).

Concerning copeptin, the mean values ranged from 4.2 to 10.3 pmol/L, excepting in the Ertan - 2020 study, where copeptin levels were much higher (30.2 pmol/L). For assessing copeptin as the exposure, the studies divided copeptin into quartiles, excepting two which divided copeptin as high and low, one based in the median (31) and the other did not report how it was divided (30). Regarding MetS diagnosis, most of the studies used the ATP III (Adult Treatment Panel III) criteria (25–27,30,31) and two studies used the IDF (International Diabetes Federation) criteria (28,29). The prevalence of metabolic syndrome in adults found in the cross-sectional and the baseline of the cohort studies ranged from 13.4 to 50.4% (27,31), and the prevalence in the study in children with obesity was 23.8% (28).

### **Relationship between copeptin and metabolic syndrome**

**Table 2** summarizes the relationship between copeptin and MetS. The Saleem - 2009 (27) cross-sectional study conducted in the USA, assessed the association of copeptin (quartiles) and metabolic syndrome in adult general population expressed by ethnicity (African Americans and non-Hispanic Whites). They found that copeptin levels in both third and fourth quartile compared with the first quartile were associated with MetS in African Americans and non-Hispanic Whites. Likewise, the Enhorning – 2011 (25) cross-sectional study conducted in the general population of Sweden, found that having higher copeptin levels (quartiles) were associated significantly with MetS. Also, they found that copeptin was associated with waist circumference, diabetes, and hyperinsulinemia. In addition, the Vintilă – 2016 (30) case-control study conducted in Romania, found a significant relationship between high copeptin levels (high vs low) and MetS. However, the other studies including Enhorning – 2013 (26), a cohort study, found no relationship between both variables.

### **Risk of bias**

Regarding the risk of bias, all cross-sectional studies met the majority of items and no study gave details about the non-respondents. The Deligözoğlu – 2020 (28) study had several additional limitations such as the lack of the representativeness of the sample, an inadequate sample size, and did not adjust for confounding factors. The cohort study had no methodological issues. On

the other hand, the case-control study misrepresented cases, had a low response rate and did not adjust for confounding factors. The results were summarized in **Table 1** and detailed in **Supplementary material 3**.

## **Discussion**

### **Main results**

A systematic review was conducted to assess the relationship between copeptin levels and MetS and included seven studies that evaluated this relationship. However, the results of the studies were inconsistent and the association was only observed in some cross-sectional studies and one case-control study. A meta-analysis could not be performed due to the heterogeneity of the designs used, diagnostic criteria for MetS and cut-off points for classification of copeptin levels.

### **Association between copeptin and MetS**

Copeptin is considered a surrogate marker for AVP, the latter being an internal environment regulating hormone, which is related to metabolic pathways that can lead to insulin resistance (25). Some experimental studies link overstimulation of AVP receptors (rV1a, rV1b and rV2) to the development of hyperglycaemia, hypertension and dyslipidaemia, which together may explain their relationship with MetS; however, the exact mechanisms by which AVP may promote the development of MetS remain unknown to date (24,25). On the other hand, AVP is an unstable metabolite and difficult to measure in blood. For this reason, copeptin proves to be a vitally important marker as it overcomes the technical difficulties of analysis and is secreted equimolar with AVP (16,17).

In assessing the included studies, we found controversy. On the one hand, some cross-sectional studies demonstrated a directly proportional association of copeptin quartiles with MetS (25,27), while other cohort and cross-sectional studies found no significant differences between groups (26,28-31). Discrepancies between results may be due to differences in statistical methods, variables selected for adjustment, criteria for MetS diagnosis, cut-off points and bioanalysis

methods for classifying and measuring copeptin. The fact that the association is observed in most cross-sectional studies suggests that copeptin may be a reliable diagnostic but not prognostic marker of MetS. On the other hand, Enhorning et al. in their cohort study found independent association of copeptin levels with abdominal obesity and T2DM, two key components of MetS; however, after adjusted analysis copeptin was shown not to be a factor associated with MetS (26). For this reason, the author suggests that the association of copeptin and MetS found in his previous cross-sectional study (Enhorning - 2011) (25) was probably driven by the association of copeptin with DM and abdominal obesity, core components of the MetS (25). However, obesity and increased glucose could be factors mediating the causal association between copeptin and MetS, so mediating factor analyses should be performed to verify this.

### **Limitations of included studies**

The included studies had a number of limitations. It should be noted that 6 of the 7 studies assessed were cross-sectional or case-control studies, so causality could not be obtained. Of the 5 cross-sectional studies, most met the items assessed in the scale, with the exception of the Deligözoğlu - 2020 study (28). The case-control study had weaknesses in the three domains of selection, comparability and exposure (30). On the other hand, the cohort study had none methodological weaknesses (26). Few studies conducted subgroup analyses and none conducted analyses of mediating factors to explain possible pathways mediating the association. Furthermore, it is important to mention that the studies do not present a standardized cut-off point to divide patients with normal or altered copeptin, but present quartiles, which vary from study to study and make meta-analysis impossible.

### **Implications and recommendations**

Copeptin has been shown to be an associated biomarker and predictor of mortality in patients with heart failure, acute coronary syndrome and acute stroke (32-34). However, its association with early metabolic disorders such as MetS, which increases the risk of cardiovascular events, is not yet fully clear. Future studies should consider standardizing cut-off points for copeptin,

bioanalysis methods, subgroup analysis, confounder adjustment and analysis of mediating factors. Finally, further evaluation of early markers of metabolic disorders and MetS is needed, as early diagnosis and intervention could reduce the risk of high morbidity and mortality cardiovascular events for the health care system.

### **Limitations and strengths**

In this review we did not perform meta-analysis or assess the certainty of the evidence due to heterogeneity among studies. However, a comprehensive search strategy was conducted with no language or publication date restrictions. In addition, all processes were performed in duplicate to reduce errors.

### **Conclusion**

The association and causal relationship between copeptin and MetS are inconsistent. Some cross-sectional and case-control studies show an association, while others find no difference, including the one included cohort study. Nevertheless, this marker may have relevance for MetS prevention and future studies should corroborate this association. Additionally, copeptin cut-off points should be standardised to define normal and altered copeptin levels.

### **Conflict of Interest**

None

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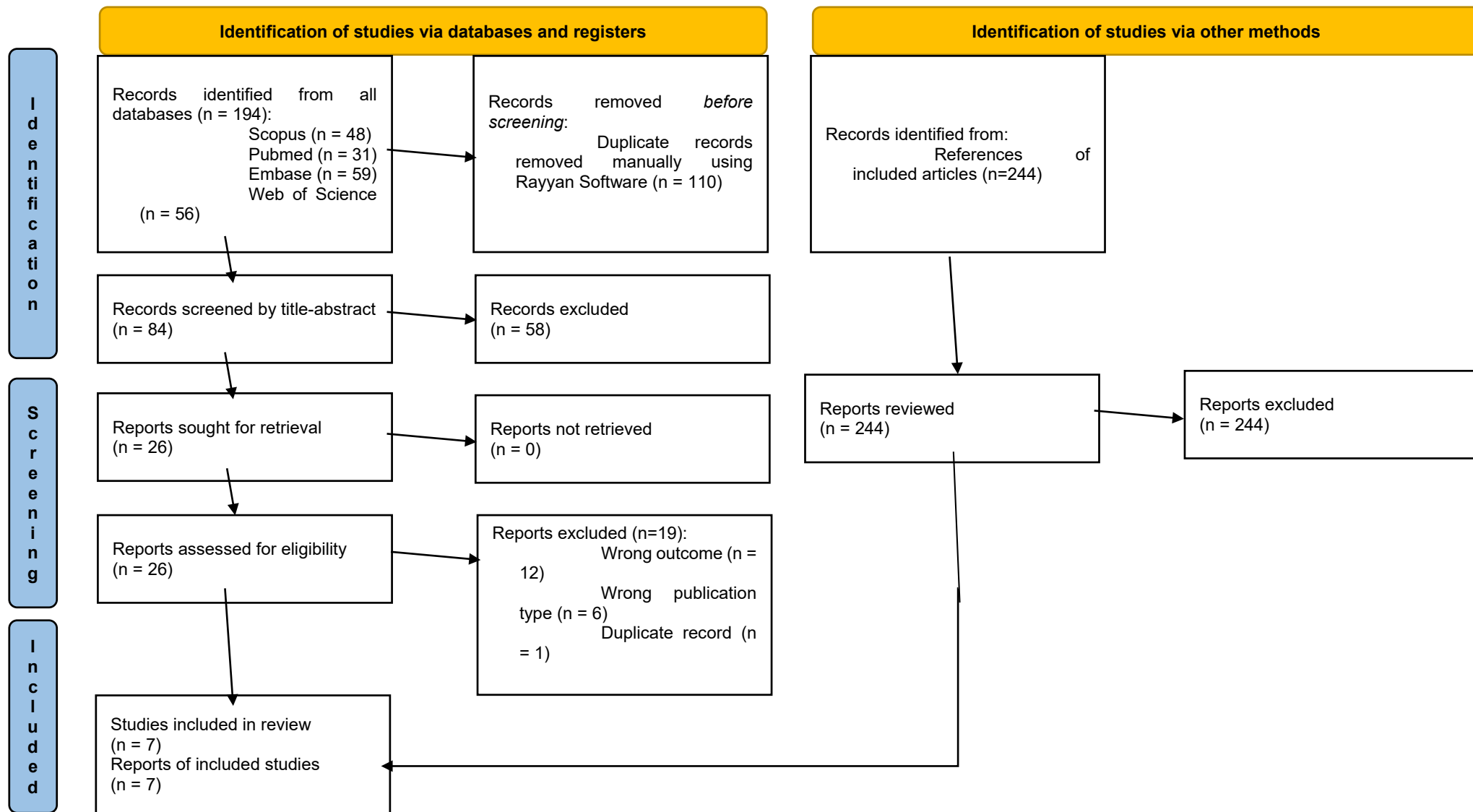
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# Tables and figures

Figure 1. Flow diagram summarizing the process of literature search and selection



**Table 1. Characteristics of included studies assessing the relationship between copeptin and metabolic syndrome (n=7).**

| Study id                    | Country     | Study design    | n    | Age (years)<br>Mean $\pm$ SD | Male sex<br>(%) | Copeptin values<br>(pmol/L)<br>Mean $\pm$ SD | MetS diagnostic<br>criteria | %<br>MetS | Quality<br>score |
|-----------------------------|-------------|-----------------|------|------------------------------|-----------------|--|-----------------------------|-----------|------------------|
| Saleem - 2009<br>(AA) (27)  | USA         | Cross-sectional | 1293 | 63.6 $\pm$ 9.3               | 28.8            | 8.6 $\pm$ 5.7 <sup>a</sup>                   | ATP-III                     | 50.4      | 9/10             |
| Saleem – 2009<br>(NHW) (27) | USA         | Cross-sectional | 1197 | 58.9 $\pm$ 10.2              | 42.6            | 5.4 $\pm$ 3.4 <sup>b</sup>                   | ATP-III                     | 48.8      | 9/10             |
| Enhörning–<br>2011 (25)     | Sweden      | Cross-sectional | 4742 | 57.5 $\pm$ 5.9               | 40.5            | 5.5 $\pm$ 3.7 <sup>b</sup>                   | ATP-III                     | 21.5      | 8/10             |
| Enhörning–<br>2013 (26)     | Sweden      | Cohort          | 1653 | NR                           | 40.9            | NR <sup>b</sup>                              | ATP-III                     | 26.2      | 9/9              |
| Then - 2015<br>(men) (29)   | Germany     | Cross-sectional | 752  | 57.4 $\pm$ 13                | 100             | 10.3 $\pm$ 4.8 <sup>c</sup>                  | IDF                         | 41.2      | 9/10             |
| Then - 2015<br>(women) (29) | Germany     | Cross-sectional | 788  | 56.2 $\pm$ 12.7              | 0               | 7.6 $\pm$ 4 <sup>c</sup>                     | IDF                         | 25.0      | 9/10             |
| Vintilă – 2016<br>(30)      | Romania     | Case control    | 105  | 50.9 $\pm$ 1.4               | 21.9            | NR <sup>c</sup>                              | ATP-III                     | 60.0      | 5/9              |
| Canivell – 2017<br>(31)     | Switzerland | Cross-sectional | 1089 | 47.4 $\pm$ 21.5              | 47              | 4.2 $\pm$ 2.4 <sup>c</sup>                   | ATP-III                     | 13.4      | 8/10             |
| Deligözoğlu–<br>2020 (28)   | Turkey      | Cross-sectional | 80   | 13.8 $\pm$ 1.93              | 44              | 30.2 $\pm$ 18.0 <sup>c</sup>                 | IDF                         | 23.8      | 4/10             |

Abbreviations: AA: African Americans, NHW: Non-Hispanic Whites, MetS: metabolic syndrome, ATP-III: Adult Treatment Panel III, IDF: International Diabetes Federation, SD: standard deviation, NR: not reported.

a. ILMA: immunoluminometric assay, b.CLIA: chemiluminescence immunoassay, c.ELISA: enzyme-linked immunosorbent assay.

**Table 2. Relationship between copeptin and metabolic syndrome.**

| Study id            | Copeptin categories values  | MetS and Copeptin (high vs low)    | Mets and copeptin (Q2 vs Q1) | Mets and copeptin (Q3 vs Q1) | Mets and copeptin (Q4 vs Q1) | Adjusted variables  |
|---------------------|---|------------------------------------|------------------------------|------------------------------|------------------------------|---|
|                     |   | Odds Ratio 95% Confidence Interval |                              |                              |                              |   |
| Saleem - 2009 (AA)  | Q1 (<5.0)<br>Q2 (5.0–8.0)<br>Q3 (8.0-12.7)<br>Q4 (>12.7)  | NE                                 | <b>1.42 (1.05 - 1.93)</b>    | <b>1.49 (1.07 - 2.06)</b>    | <b>2.07 (1.45 - 2.95)</b>    | Age, sex, creatinine, smoking, statin or diuretic use, history of myocardial infarction/stroke, physical activity, educational status |
| Saleem - 2009 (NHW) | Q1 (<3.3)<br>Q2 (3.3-5.0)<br>Q3 (5.0-7.9)<br>Q4 (>7.9)  | NE                                 | 1.12 (0.79 - 1.59)           | <b>1.79 (1.27 - 2.51)</b>    | <b>1.74 (1.21 - 2.50)</b>    |   |
| Enhörning - 2011    | Men:<br>Q1 (<4.6)<br>Q2 (4.6–7.1)<br>Q3 (7.1–10.6)<br>Q4 (10.7–4.3)<br>Women:<br>Q1 (<2.7)<br>Q2 (2.7–4.2)<br>Q3 (4.3–6.4)<br>Q4 (6.5–14.3) | NE                                 | <b>1.55 (1.25 - 1.93)</b>    | <b>1.82 (1.47 - 2.25)</b>    | <b>1.93 (1.57 - 2.39)</b>    | None  |
| Enhörning - 2013    | NR  | NE                                 | 1.21 (0.85 - 1.72)           | 1.05 (0.74 - 1.49)           | 1.34 (0.95 - 1.91)           | Follow-up time, age, sex, cystatin C, hypertension, glucose, triglycerides, HDL, waist circumference                                  |
| Then - 2015 (men)   | NR  | NE                                 | NE                           | NE                           | 1.13 (0.72 - 1.76)           | Age, history of myocardial infarction/ stroke, smoking, alcohol intake, physical activity   |
| Then - 2015 (women) | NR  | NE                                 | NE                           | NE                           | 1.11 (0.68 - 1.83)           |   |
| Vintilä - 2016      | Low (0.1-196.4)<br>High (196.5-455.1)   | <b>20 (3.03 - 131.7)</b>           | NE                           | NE                           | NE                           | None  |
| Canivell - 2017     | NR  | 1.12 (0.74 - 1.69)                 | NE                           | NE                           | NE                           | Age, sex, center, socioeconomic status, intake of fruits and vegetables,  |

|  |  |    |    |                    |                    |   |
|--|--|----|----|--------------------|--------------------|---|
|  |  |    |    |                    |                    | physical activity, alcohol intake, smoking, testosterone, estradiol daytime urinary excretion |
| Deligözoğlu - 2020   | Q1 (<17.0)<br>Q2 (17.0-26.4)<br>Q3 (26.6-40.0)<br>Q4 (40.3-95.0) | NE | NE | 0.86 (0.22 - 3.28) | 0.33 (0.06 - 1.43) | None  |
| Abbreviations: AA: African Americans, NHW: Non-Hispanic Whites, MetS: metabolic syndrome, SD: standard deviation, NR: not reported, NE: not evaluated. Significant values in bold. |  |    |    |                    |                    |   |

## Anexos

**Evidencia de sumisión del artículo en una revista de prestigio**

Manuscript submitted to Journal of Nutrition and Metabolism Recibidos x



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Dear Dr. Galindo-Yllu ,

The manuscript titled "Association between copeptin and metabolic syndrome: a systematic review" has been submitted to Journal of Nutrition and Metabolism by David R. Soriano-Moreno.

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# Copia de la resolución de inscripción del perfil de proyecto de tesis en formato artículo aprobado por el consejo de facultad correspondiente

  
"Año del Bicentenario del Perú: 200 años de Independencia"  
*Una Institución Avanzada*

**RESOLUCIÓN N° 2640-2021/UPEU-FCS-CF**  
Lima, Ñaña, 09 de noviembre de 2021

**VISTO:**  
El expediente de **BRENDA MIREYA GALINDO YLLU**, identificada con código universitario N° 201520268, de la Escuela Profesional de Medicina, de la Facultad de Ciencias de la Salud de la Universidad Peruana Unión;

**CONSIDERANDO:**

Que la Universidad Peruana Unión tiene autonomía académica, administrativa y normativa, dentro del ámbito establecido por la Ley Universitaria N° 30220 y el Estatuto de la Universidad;

Que la Facultad de Ciencias de la Salud de la Universidad Peruana Unión, mediante sus reglamentos académicos y administrativos, ha establecido las formas y procedimientos para la aprobación e inscripción del perfil de proyecto de tesis en formato artículo y la designación o nombramiento del asesor para la obtención del título profesional;



Que **BRENDA MIREYA GALINDO YLLU**, ha solicitado: la inscripción del perfil de proyecto de tesis titulado *La coceptina en el síndrome metabólico: una revisión sistemática y un metaanálisis*; y la designación del Asesor, encargado de orientar y asesorar la ejecución del perfil de proyecto de tesis en formato artículo;



Estando a lo acordado en la sesión del Consejo de la Facultad de Ciencias de la Salud de la Universidad Peruana Unión, celebrada el 09 de noviembre de 2021, y en aplicación del Estatuto y el Reglamento General de Investigación de la Universidad;

**SE RESUELVE:**

Aprobar el perfil de proyecto de tesis en formato artículo titulado *La coceptina en el síndrome metabólico: una revisión sistemática y un metaanálisis*; y disponer su inscripción en el registro correspondiente, designar al Dr. **SALOMÓN HUANCAHUIRE VEGA**, para que oriente y asesore la ejecución del perfil de proyecto de tesis en formato artículo el cual fue dictaminado por el *Mtro. Luis Felipe Segura Chávez* y el *Mg. Pool Marcos Carbajal*, otorgándoles un plazo máximo de doce (12) meses para la ejecución.

Regístrese, comuníquese y archívese.

  
 **Dr. Roger Albornoz Esteban**  
DECANO

  
 **Msc. Mary Luz Solorzano Aparicio**  
SECRETARIA ACADÉMICA

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# Carta de aprobación de comité de ética



*Una Institución Adventista*

Lima, Ñaña, 30 de noviembre de 2021

## EL COMITÉ DE ÉTICA DE INVESTIGACIÓN DE LA FACULTAD DE CIENCIAS DE LA SALUD

### CONSTA

Que el proyecto de investigación de **Brenda Mireya Galindo Yllu**, identificada con DNI No. **74525691**, su asesor **Salomon Huanchuire Vega**, identificado con DNI No. **41407030**, con el título: **"La copeptina en el síndrome metabólico: una revisión sistemática y un metaanálisis"**, fue evaluado y aprobado por el Comité de Ética de Investigación de la Universidad Peruana Unión, considerando su calidad científica, consideración del bienestar de sus participantes, y conformidad con los estándares de la ética establecidas en el Código de ética para la Investigación de la Universidad Peruana Unión.

Para mantener la aprobación del Comité de Ética, se tiene que cumplir con los siguientes requisitos:

- 1) Cada participante debe dar consentimiento informado. En el caso de menores de edad, por lo menos uno de sus padres o guardianes debe registrar su consentimiento informado y el menor de edad debe registrar su asentimiento informado, en caso de trabajos prospectivos. En caso de trabajos retrospectivos contar con la carta de autorización de la institución.

Los resultados de este proyecto puedan ser publicados con referencia a aprobación Número 2021-CE-FCS - UPeU-00339.



**M<sup>ra</sup>. María Magdalena Díaz Orihuel**

Presidenta del Comité de Ética de Investigación



**Psic. Justas Trinidad Ticso**

Secretaria del Comité de Ética de Investigación