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# Insulin-resistance conditions as risk factors for Acanthosis nigricans: A systematic review and meta-analysis

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## ABSTRACT

*Background:* Acanthosis nigricans (AN), a dermatological condition, is characterized by dark velvety discoloration and thickening of the skin. It has been known to be associated with various insulin-resistant conditions; however, risk factors of AN are not fully established. *Methods:* We conducted a systematic search of the literature using various combinations of specific keywords. The odds ratio (OR) and their 95% CI were used to draw forest plots. *Results:* In total, 37 studies were included in this meta-analysis. The combined meta-analysis yielded an OR of 0.35 with a 95% CI of 0.19–0.64 and a *P* value of .0006. The type 2 diabetes mellitus (T2DM)-related studies had an overall effect size of OR 0.24 with a 95% CI of 0.10–0.59 and a *P* value of .002. For obesity-related studies, the overall effect size was OR 0.62 with a 95% CI of 0.23–1.63 and a *P* value of .33. PCOS-related studies yielded an OR of 0.34 with a 95% CI of 0.07–1.59 and a *P* value of .17. Finally, the studies on acromegaly had an effect size of -0.17 with a 95% CI varying from -0.42 to 0.008 and a *P* value of .19. *Conclusion:* Insulin-resistance conditions such as T2DM, obesity, PCOS, and acromegaly are important risk factors for the development of AN when their effect size is combined with strong statistical significance. However, only T2DM shows a strong statistical significance; as a risk factor for AM when these conditions are taken individually.

**Keywords:** Acanthosis nigricans, meta-analysis, PCOS, melanin pigmentation, diabetes mellitus

## 1. BACKGROUND

Acanthosis nigricans (AN), a dermatological condition characterized by thickening of the skin and subsequent darkening, has been associated with hyperinsulinemia (Stuart et al., 1994). The darkening of the skin is not due to an increase in melanin pigmentation; instead, it is due to hyperkeratosis. The neck is involved in more than 90% of the cases; other areas such as the knee,



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axilla, and elbows can also be affected in some cases (Burke et al., 1999; Stuart et al., 1998). It is more common in patients with obesity and diabetes. It usually occurs in younger individuals (<40 years of age) and is mostly asymptomatic. It mostly affects American Indians, although it is also common in Africans, Caucasians, and Hispanics. Asians have been found to be rarely affected by this condition (Popa et al., 2019). Its prevalence varies from 7% to 74% based on the population, age group, and race (Sayarifard et al., 2017; Dassanayake et al., 2011; Kong et al., 2010). AN is classified in many ways, and the most common method involves using a 0–4 severity scale depending on how many areas are affected. There is currently no treatment option available to directly treat AN, although medications are available to treat its underlying effects on the skin color and texture (Patel et al., 2018). Although a few types are considered hereditary and are inherited as an autosomal dominant trait, AN is mostly acquired.

Even though many studies have found AN to be associated with malignancy, its relation with various insulin-resistant conditions such as metabolic syndrome, type 2 diabetes mellitus (T2DM), polycystic ovary syndrome (PCOS), and obesity is now recognized (Kong et al., 2007). The pathophysiology of AN involves a complex mechanism with intricate steps (Torly et al., 2002). Insulin regulates the metabolism of proteins, carbohydrates, and fats at low concentrations and helps promote the growth of cells by binding to insulin receptors. When insulin concentration becomes too high, it begins to bind to insulin-like growth factor receptor 1 (IGF-1R), which is similar to insulin receptors. This binding promotes the growth of epidermal cells, leading to the proliferation of fibroblasts and keratinocytes and resulting in AN (Jeong et al., 2010). High concentrations of insulin cause AN directly, as discussed above, or indirectly by increasing the IGF-1R levels, promoting cell growth and cell differentiation (Phiske, 2014).

Insulin resistance has been found in conditions such as diabetes mellitus, obesity, PCOS, and various metabolic disorders (Hermanns-Lé et al., 2004). Many studies have indicated these insulin-resistance conditions as risk factors for developing AN. However, the results vary in terms of how strongly these conditions are associated with the development of AN. Furthermore, no meta-analysis has been performed so far on the topic. The present study systematically evaluates the relation between insulin-resistance conditions and the development of AN and summarizes the results in a meta-analysis. The study also determines the prevalence of AN under different insulin-resistance conditions.

## 2. METHODOLOGY

The study was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA). Literature search strategy: A comprehensive review of the literature on Pubmed, Google Scholar, ISI Web of Knowledge, and Science Direct was carried out. The literature search was conducted between 5 December 2019 and 17 January 2020. The following insulin-resistance conditions were investigated as the risk factors: diabetes mellitus, obesity, PCOS, metabolic syndrome, and acromegaly. All studies showing an association between these risk factors and AN were considered. The keywords used in different combinations for search purposes were “acanthosis nigricans,” “risk factors,” “insulin resistance,” “diabetes mellitus,” “PCOS,” “polycystic ovarian syndrome,” “metabolic syndrome,” and “acromegaly.” The generated results were screened based on the titles and abstracts. Any duplicated articles were removed.

### Inclusion and exclusion criteria

Articles showing any association of a risk factor with the development of AN were included in the review. The following types of articles were included: case-control, cohorts, and cross-sectional studies. All the articles were in English and contained data for risk factor calculation. Case reports, articles not available in the English language, and articles that did not provide the data as a measure of risk factors were excluded.

### Data extraction

Two investigators independently selected the articles based on the aforementioned inclusion and exclusion criteria. If the number of articles selected by the investigators was found to be different, a consensus was reached following discussion. Both investigators also independently reviewed full texts of articles and extracted the relevant information in excel sheets. A third investigator reviewed the extracted information for any discrepancy.

The following information related to the studies was extracted: authors, publication date, study design, country, and sample size. The following characteristics of patients were considered: age, gender, type of insulin-resistance condition, and race (if available). Finally, the prevalence of AN, odds ratio (OR) with 95% confidence interval (CI), and *P* values were extracted from each study.



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Assessment of quality and grading: Two investigators independently assessed the quality of the studies included in this meta-analysis. The Newcastle–Ottawa scale (NOS) was used to determine the quality of the articles. Articles with a score of >7 were considered to be of high quality and those with a score of 5–7 were taken to be of moderate quality (Stang, 2010).

**Statistical analysis**

The OR was taken from the case-control studies and was converted into the hazard ratio (HR). The OR with 95% CI was used to draw forest plots in meta-analysis. The heterogeneity was investigated using $X^2$ and $I^2$ tests; $I^2$>50% was considered as the presence of heterogeneity in studies (Higgins and Thompson, 2002; Higgins et al., 2003). A random-effect model was applied to nullify the effect of heterogeneity. The publication bias was accessed using funnel plots. The statistical analysis was performed using the Review Manager 5.4 software.

## 3. RESULTS

The literature search yielded 980 articles. After screening the abstracts and titles, 300 articles were identified as appropriate. Next, full-text reviews and removal of duplications were performed, which left 37 articles for inclusion in the final quantitative analysis. The search results are summarized in a PRISMA diagram (Fig. 1).

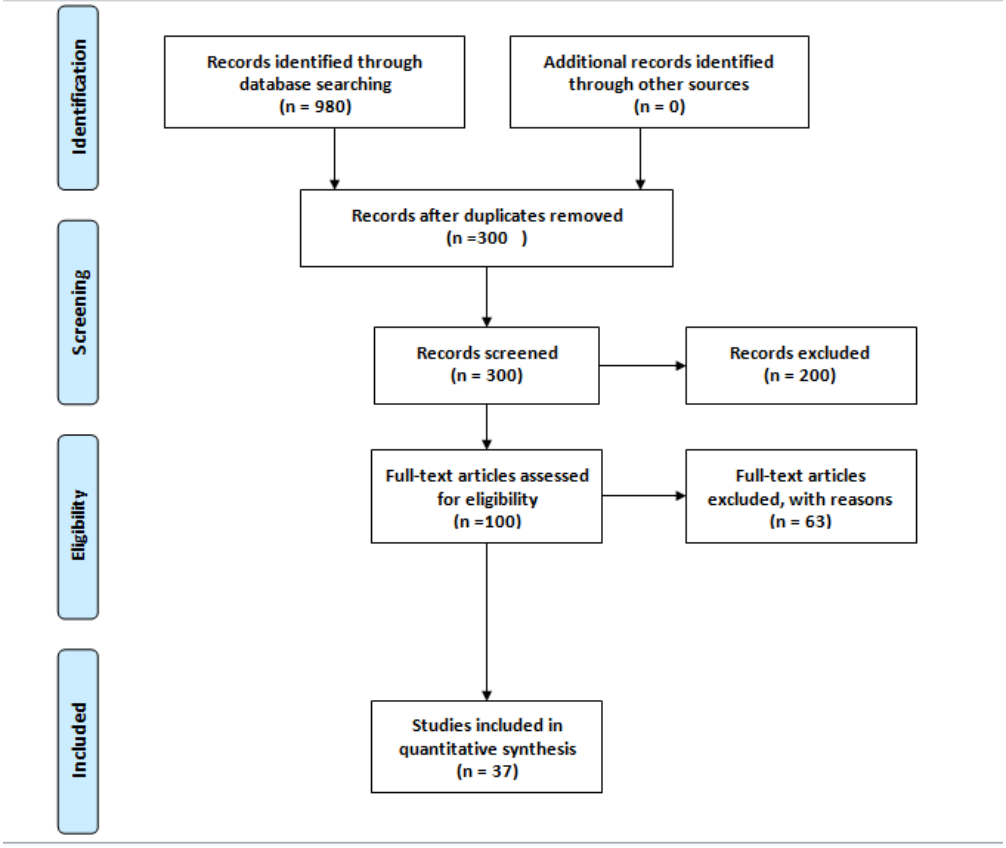


**Figure 1** Summary of the literature search process.

**Study and patient characteristics**

In total, 37 studies were considered in this review. Of these, 13 were on patients with obesity-related conditions, 10 on patients with diabetes mellitus, 6 on patients with PCOS, and 8 on acromegaly patients. Most of the studies (27) were cross-sectional, 2 were case controls, and 1 was retrospective. Of these, 8 studies were conducted in the US, 2 in India, 5 in Japan, 10 in Africa, and 2 each in Pakistan, Italy, and China. The cross-sectional studies had 7895 patients with diabetes, 3132 patients with obesity-related conditions, 632 patients with PCOS, and 1112 patients with acromegaly. The total number of patients in all studies was 11971. In these studies, the prevalence of AN ranged from 9.8% to 68%.A quality assessment was carried out, and 23 studies were found to be of high quality with a score >7, and 14 studies were of moderate quality with a score of 5–7.



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There were 10 studies on diabetes-related conditions. The total number of patients was 78895, among which 56% were women, and 44% were men. Most of the patients were African Americans and Hispanics. The mean age of the patients was 45.36 years. Table 1 summarizes the study and patient-related information.

**Table 1** Characteristics of the study and patients in studies on diabetes.

| Study ID | First Authors | Publication year | Sample size | Study design | Insulin-resistance condition | Patient characteristics | AN prevalence |
|---|---|---|---|---|---|---|---|
| 1 | Bahadursingh | 2014 | 311 | cross-sectional | Type 2 diabetes | Mean age in years (SD): 58.1 (12.6); Females: 55.6% | 52.7% (95% CI 47.2, 58.3) |
| 2 | Grandhe | 2005 | 150 subjects 150 controls | case control | Type 2 diabetes | Mean age in years (SD) Case: 52.2 (10.8) Control: 49.9 (11.6) | Patients with diabetes: 62.6% Healthy controls: 40% |
| 3 | Ogbera | 2009 | 347 | cross-sectional | Type 2 diabetes | Mean age in years: 57.3+11.8 | 17% |
| 4 | Litonjua | 2003 | 216 | retrospective | Type 2 diabetes | Mean age in years with AN: 36.9±13.8 Mean age in years without AN: 34.1±10.1 | 36.1% |
| 5 | Kong | 2007 | 1,133 | cross-sectional | Type 2 diabetes | Data not available | Children: 17% Adults: 21% |
| 6 | Barrett | 2016 | 276 | cross-sectional | Type 2 diabetes | Mean age in years: 17.3±0.5 | 44.20% |
| 7 | Hoffmann | 2015 | 390 | cross-sectional | Type 2 diabetes | Mean age in years with AN: 46.9 Mean age in years without AN: 50 | 30% |
| 8 | Stoddart | 2002 | 2205 | cross-sectional | Type 2 diabetes | Mean age in years: 22.1 Age group and their numbers 7–19: 143 (8.3%) 20–39: 497 (28.7%) 40–65: 1090 (63.0%) | 34.20% |
| 9 | Kong | 2010 | 1730 | cross-sectional | Type 2 diabetes | Females (mean age in years): 1204 (69.6) Males (mean age | 19.40% |



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|---|---|---|---|---|---|---|---|
| | | | | | | in years): 526 (30.4)<br>Race/Ethnicity (AN incidence)<br>African American: 362 (20.9)<br>Hispanic: 714 (41.3)<br>White, non-Hispanic: 531 (30.7)<br>Others*: 123 (7)<br>Females: 52.4%<br>Mean age in years: 13.5<br>Majority of the students (99.5%) were between 12 and 15 years of age. | |
| 10 | Mukhtar | 2001 | 675 | cross-sectional | Type 2 diabetes and obesity | Race/Ethnicity (AN incidence)<br>Hispanic: 46.5%<br>American Indians: 19%<br>Obese: 26.8% At least one parent with diabetes: 11.3% | 18.90% |

There were 13 studies on obesity-related conditions with 3132 patients. Of these, 39% were men, and 61% were women. The mean age of the patients was 23.62 years. The characteristics of these studies and the patients are summarized in Table 2.

Only 6 studies were on PCOS. The total number of patients was 632. The mean age of the patients was 36.29 years. The characteristics of the patients and these studies are summarized in Table 3.

There were 8 studies on acromegaly and AN, with 1112 patients. Of these, 42% were women and 58% men. The mean age was 32.31 years. Table 4 summarizes the study and patient-related characteristics of acromegaly studies.

**Table 2** Characteristics of the study and patients in studies on obesity-related conditions.

| Study | First Authors | Publication | Sample | Study | Insulin- | Patient | AN |
|---|---|---|---|---|---|---|---|



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| ID | | year | size | design | resistance condition | characteristics | prevalence |
|---|---|---|---|---|---|---|---|
| 1 | Hud | 1992 | 34 | cross-sectional | Obesity | - | 74% |
| 2 | Kluczynik | 2011 | 194 | cross-sectional | Obesity | Males: 66 (34%)<br>Females: 128 (66%)<br>Race/Ethnicity<br>White: 71 (36.1%)<br>Brown-skinned: 122 (63.4%)<br>Indigenous: 1 (0.5%)<br>Age group<br>Preschoolers: 18 (9.3%)<br>School-aged: 57 (29.4%)<br>Adolescent: 119 (61.3%) | 58.20% |
| 3 | Palhares | 2017 | 172 | cross-sectional | Obesity | - | 51.10% |
| 4 | Lopez-Alvarenga | 2020 | 670 | cross-sectional | Obesity | Girls: 670 (49.3%)<br>Mean age in years: 11.5±3.5<br>BMI (kg/m$^2$): 24.7±6.5 | 65% |
| 5 | Hudson | 2017 | 174 | cross-sectional | Obesity | Mean age in years (SD) 15.4 (2.1)<br>AN predominance at later stages of puberty: 12% pre/early, 22% mid, 66% late/complete<br>Females: 62%<br>Race/Ethnicity<br>White: 38%<br>Black: 30%<br>South Asian: 21%<br>Mixed/other: 11% | 63% |



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|---|---|---|---|---|---|---|---|
| 6 | Chang | 2008 | 4033 | cross-sectional | Obesity | Boys: 2117<br>Girls: 1916<br>Mean age in years: 10.9±0.6<br>Mean BMI: 8.6±3.3 kg/m | Boys: 8.4%<br>Girls: 5.1% |
| 7 | Alazab | 2015 | cases: 250<br>control: 250 | case control | Obesity | Mean age in years (Mean±SD):<br>25–60 (39.2±6.8)<br>18–60 (33.4±7.8)<br>0.00*<br>Case<br>Males: 36 (14.4%)<br>Females: 214 (85.6%)<br>Control<br>Males: 38 (15.2%)<br>Females: 212 (84.8%) | 53.60% |
| 8 | Rafalson | 2011 | 854 | cross-sectional | Obesity | Mean age in years 11.4±3.3<br>Mean BMI ($kg/m^2$): 28.8±6.8<br>Females/Males (%): 61/39 | 26.60% |
| 9 | Scott | 2010 | 142 | cross-sectional | Obesity | Mean age in years: 12.4±2.6<br>BMI ($kg/m^2$): 40.5±9.8 | 68% |
| 10 | Dubnov-Raz | 2011 | 149 | cross-sectional | Obesity | Mean age in years (SD): 9.75 (6.0–12.3)<br>Weight in kg (SD): 65.3 (43.5–80.4)<br>Males (n, % ): 8 (36%) | 14.80% |
| 11 | Ayaz | 2014 | 250 | cross-sectional | Obesity | Mean age in years: 25.03<br>BMI ($kg/m^2$): 34.9–10.69 | 40% |



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|---|---|---|---|---|---|---|---|
| 12 | Ng | 2014 | 543 | cross-sectional | Obesity | Age group and their numbers: All 543 [12±3] 5–11 251 (46%) [10±2] 12–18 292 (54%) [14±2] Males: 346 (64%) Females: 197 (36%) BMI Overweight: 90–97% 124 (23%) Obese: >97% 419 (77%) | 63% |
| 13 | Brickman | 2007 | 618 | cross-sectional | Obesity | Mean age in years: 11.5 Females: 51% Race/Ethnicity African American: 61% Hispanic: 27% Caucasian: 12% BMI with ‡95th percentile: 32% | 18.60% |

**Table 3** Characteristics of the study and patients in studies on PCOS.

| Study ID | First Authors | Publication year | Sample size | Study design | Insulin-resistance condition | Patient characteristic | AN prevalence |
|---|---|---|---|---|---|---|---|
| 1 | Folant P | 2011 | 26 | cross-sectional | PCOS | Mean age in years: 29.38 | 39% |
| 2 | Dong | 2013 | 339 | cross-sectional | PCOS | Mean age in years (SD): 26 (24–28%) BMI (kg/m$^2$) (SD): 20.0 (18.8–21.5) | 9.70% |



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| 3 | Khan | 2016 | 98 | cross-sectional | PCOS | Mean age in years: 31.26 | 33.30% |
| 4 | Michaele | 2017 | 44 | cross-sectional | PCOS | Mean age in years: 32.33 | 42% |
| 5 | Keen | 2020 | 100 | cross-sectional | PCOS | Mean age in years: 25.18±3.61 BMI (kg/m$^2$): 26.95±4.50 | 30% |
| 6 | Lugo | 2004 | 32 | cross-sectional | PCOS | Mean age in years: 33.36 | 68.75% |

**Table 4** Characteristics of the study and patients in studies on acromegaly.

| Study ID | First Authors | Publication year | Sample size | Study design | Insulin-resistance condition | Patient characteristics | AN prevalence |
|---|---|---|---|---|---|---|---|
| 1 | Fernando Cordido | 2013 | 96 | cross-sectional | Acromegaly | Mean age in years: 26.28 Females: 56% Males: 44% | 39.30% |
| 2 | Akiyama | 2014 | 396 | cross-sectional | Acromegaly | Mean age in years: 30.26 Females: 48% Males: 58% | 28.45% |
| 3 | Stratakis | 1998 | 200 | cross-sectional | Acromegaly | Mean age in years: 27.23 Females: 49.5% Males: 51.5% | 27.70% |
| 4 | Abbasid | 2015 | 122 | cross-sectional | Acromegaly | Mean age in years: 33.69 Females: 37% Males: 63% | 43% |
| 5 | Stones | 2013 | 89 | cross-sectional | Acromegaly | Mean age in years: 29.63 Females: 63% Males: 37% | 26.70% |



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|---|---|---|---|---|---|---|---|
| 6 | Mustaqeem | 2018 | 103 | cross-sectional | Acromegaly | Mean age in years: 36.36 Females: 47.5% Males: 52.5% | 29% |
| 7 | Frank | 2018 | 26 | cross-sectional | Acromegaly | Mean age in years: 28.89 Females: 59% Males: 41% | 33% |
| 8 | Pobara | 2010 | 166 | cross-sectional | Acromegaly | Mean age in years: 31.36 Females: 38% Males: 62% | 42% |

**Meta-analysis**

The meta-analysis of all the conditions shown as a forest plot is depicted in Fig. 2. Overall, the OR was 0.35 with a 95% CI of 0.19–0.64. Here, 8 studies were statistically significant for the non-AN group, while 17 were significant for the AN group. The remaining studies were insignificant. The overall effect size was significant for the AN group, implying that the insulin-resistance conditions are risk factors for AN (*P*=.0006).

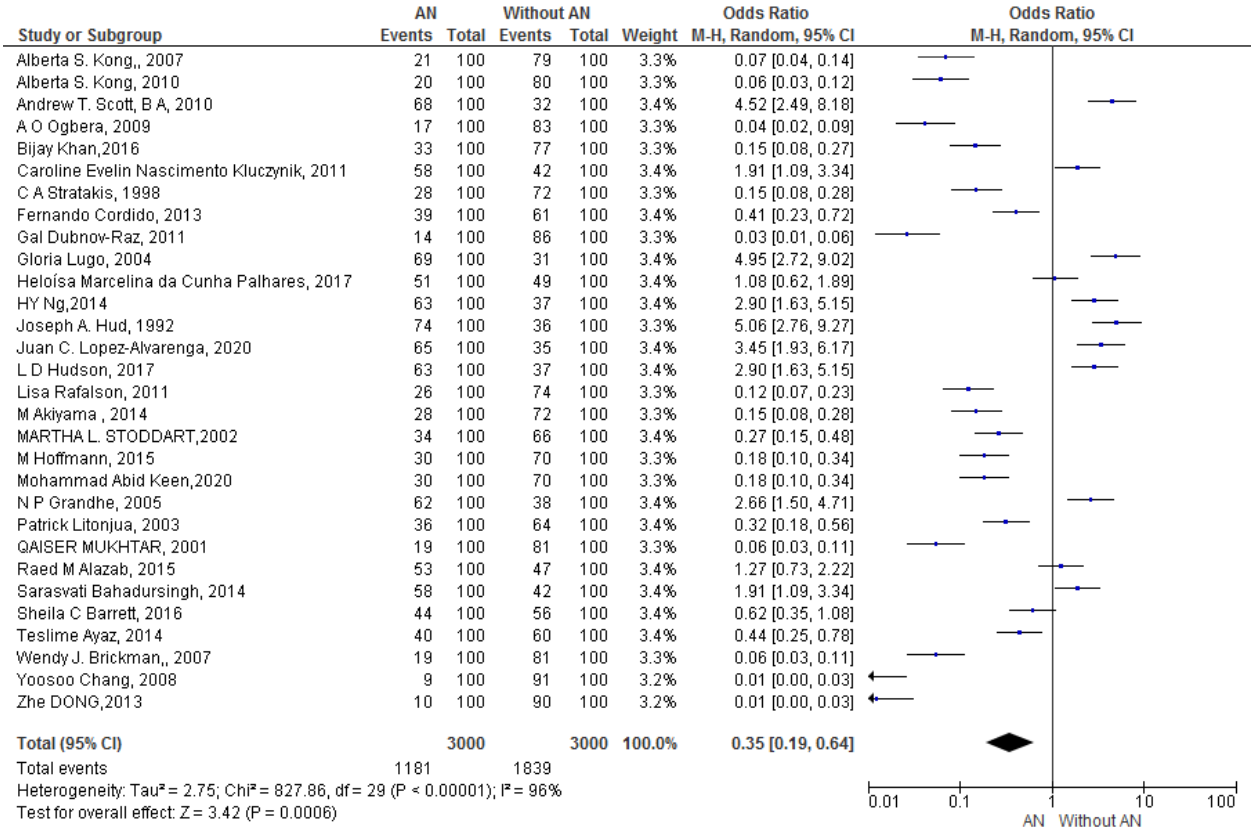


**Figure 2** Meta-analysis of all conditions as risk factors for acanthosis nigricans (AN).



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**Diabetes mellitus as a risk factor for AN**

When only diabetes-related studies were analyzed in the meta-analysis, an overall effect size of 0.24 was found with a 95% CI of 0.10–0.59. Two studies were statistically significant for the non-AN group, while the remaining 8 were significant for the AN group. Overall, diabetes mellitus was a risk factor for AN with a *P* value of .002 (Figure 3).

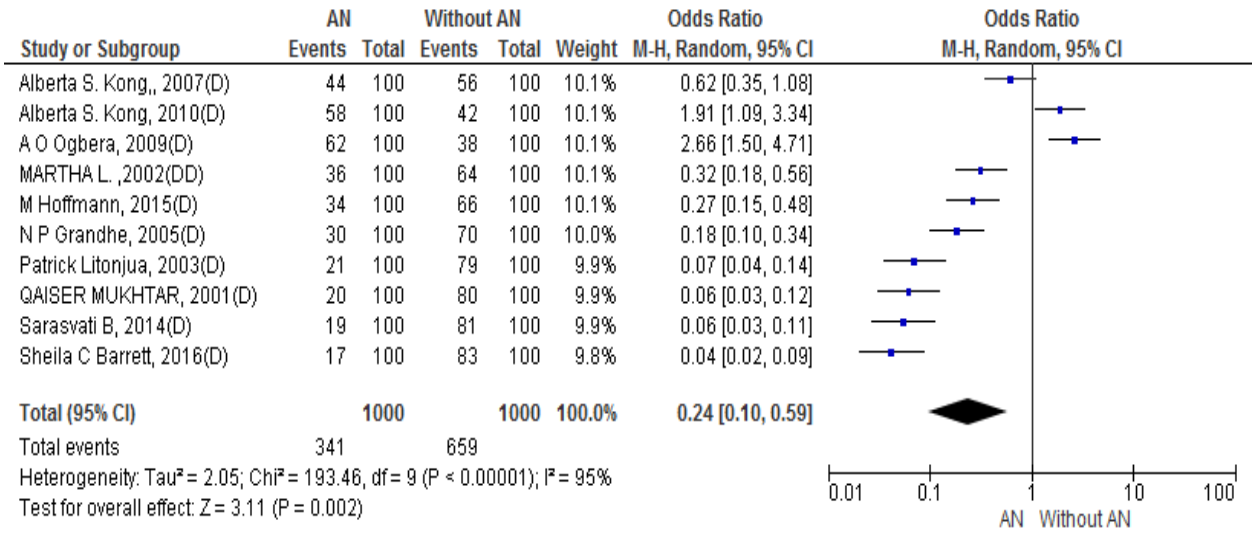


**Figure 3** Meta-analysis of diabetes mellitus as a risk factor for acanthosis nigricans (AN).

**Obesity as a risk factor for AN**

When only obesity-related studies were analyzed in the meta-analysis, the overall effect size was found to be 0.62 with a 95% CI of 0.23–1.63. Five of these studies were statistically significant for the non-AN group, while another five were significant for the AN group. The remaining three studies were insignificant. Overall, obesity was not a risk factor for AN (*P*= .33, Figure 4).

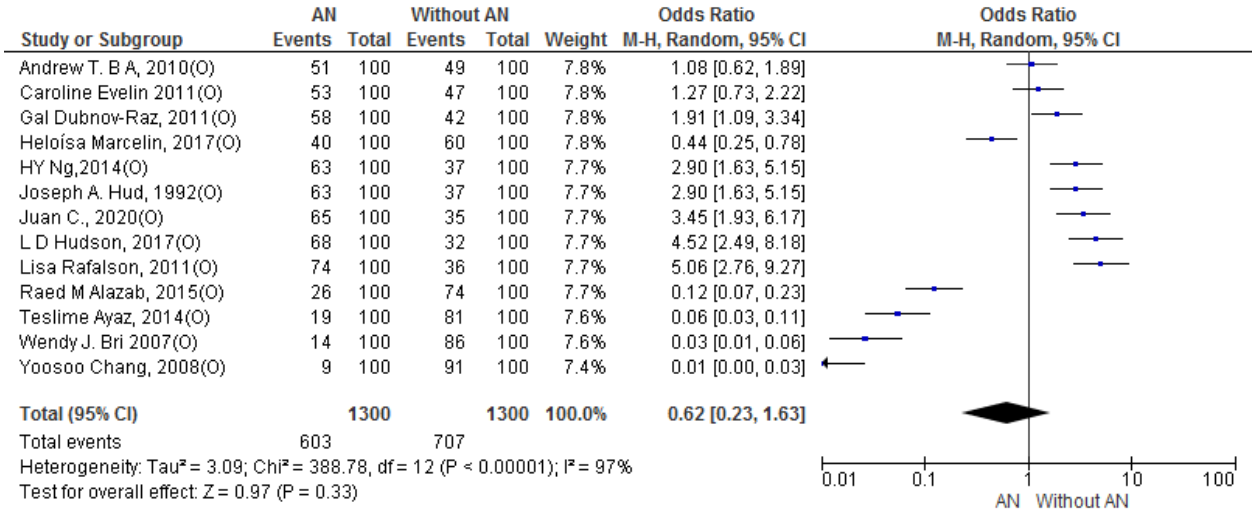


**Figure 4** Meta-analysis of obesity as a risk factor for acanthosis nigricans (AN).

**PCOS as a risk factor for AN**

When only PCOS-related studies were analyzed in the meta-analysis, the overall effect size was 0.34 with a 95% CI of 0.07–1.59. Two of these studies were statistically significant for the non-AN group, while 4 were significant for the AN group. We found PCOS as a risk factor for AN with a *P* value of .17 when all the study results were considered together (Figure 5).



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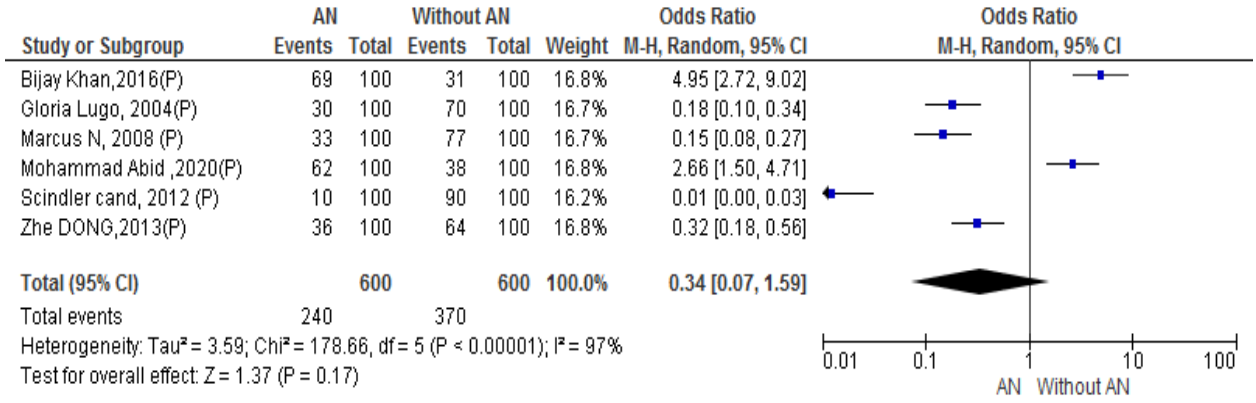


**Figure 5** Meta-analysis of PCOS as a risk factor for acanthosis nigricans (AN).

**Acromegaly as a risk factor for AN**

When only acromegaly-related studies were analyzed in the meta-analysis, the overall effect size was -0.17 with a 95% CI value varying from -0.42 to 0.008. Two of these studies were statistically significant for the non-AN group, while 5 were significant for the AN group. However, when we combined the overall effect size, we found acromegaly as a risk factor for AN (*P*= .19, Figure 6).

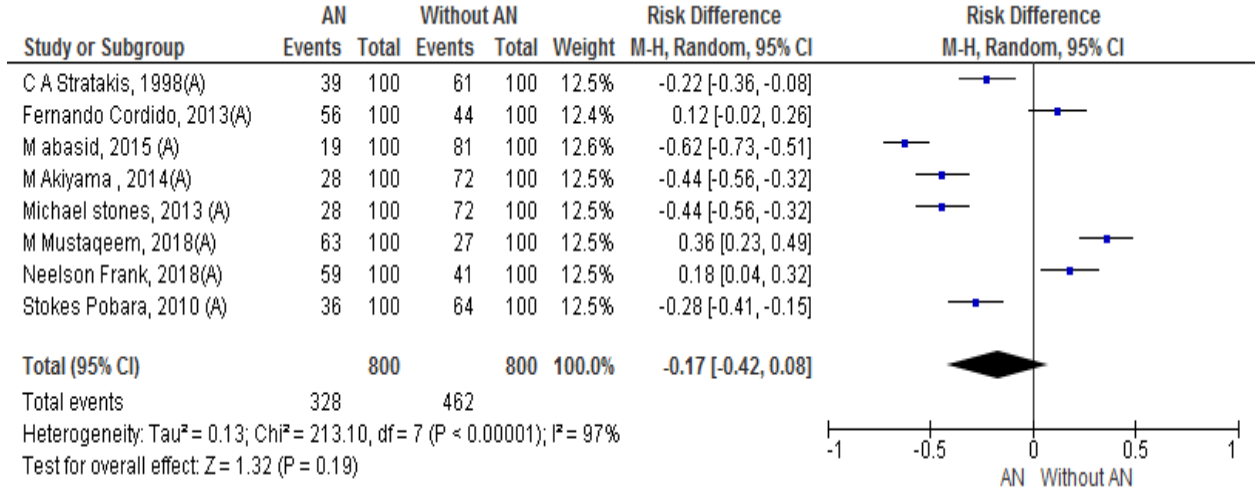


**Figure 6** Meta-analysis of acromegaly as a risk factor for acanthosis nigricans (AN).

## 4. DISCUSSION

The present meta-analysis investigates how strongly insulin-resistance conditions (i.e., diabetes mellitus, obesity, PCOS, and acromegaly) are linked as risk factors for the development of AN. This is the first meta-analysis conducted on the topic. We were able to obtain 37 studies, a high number, for inclusion in this meta-analysis. AN, a dermatologic condition characterized by hyperkeratosis and papillomatosis, has been shown to be a reliable marker of hyperinsulinemia and diabetes mellitus. This meta-analysis demonstrated that the previously mentioned 4 insulin-resistance conditions are risk factors for the development of AN when the effect size of all the studies with different insulin-resistance conditions are combined (*P*=.0006). This result is consistent with the findings of other studies that showed that insulin resistance is common in individuals with AN (Chueh et al., 2007; Kahn et al., 1976; Patidar et al., 2012). AN occurs under two conditions: when the insulin concentration is too high or when the levels of insulin-like growth factor receptors are too low. Both these conditions result in the accumulation of insulin, leading to the proliferation and thickening of keratocytes (Hermanns-Lé et al., 2004).

We performed a separate meta-analysis for each insulin-resistant condition and found a strong association of diabetes mellitus as a risk factor for AN (*P*=.002). Our findings are in good accord with those of other studies (Ogbera et al., 2009; Litonjua et al., 2004; Kong et al., 2007). In addition, we found an overall prevalence of 44% for AN in all studies on diabetes. We found diabetes as a risk factor for AN, some studies have reported an opposite result and noted AN as a risk factor for diabetes mellitus (Stuart et al., 1994, 1998). AN has also been used as an assessment criterion for T2DM risk analysis (American Diabetes Association, 2004).



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Furthermore, our findings show that more women are affected by AN than men. We did not find any statistically significant association of obesity as a risk factor for AN development. The studies that we considered reported conflicting results, with half of them listing obesity as a risk factor for AN, while the other half did not find any association. When we combined the effect size of all these studies, the overall results were insignificant ($P$= .38). The prevalence of AN in all studies on obesity-related conditions was 39%. These studies also showed that metabolic syndrome is common in childhood obesity and AN can be used as an external marker to predict the metabolic syndrome in such cases. Note that studies conducted in different parts of the world have shown the same role of AN, especially in young children with obesity (Hud, 1992; Chang, 2008).

Our analysis did not show any significant association between PCOS and AN. The prevalence of AN in all studies on PCOS was 33.9%. PCOS is a common endocrine disorder and is linked to insulin resistance (Dunaif, 1997). Similarly, our analysis did not find any statistically significant association between acromegaly and AN. Our study has some limitations as well. First, most of the studies conducted on the subject are cross-sectional and very few are case-control. The evidence presented by cross-sectional studies is of poorer quality compared to that presented by case-control studies. Besides, the studies were heterogeneous and analyzed either all insulin-resistance conditions simultaneously or separately in groups. Although the studies considered here had a number of confounding variables such as gender, age, and ethnicity, we did not perform a subgroup analysis based on these variables, which can affect the results. Finally, the studies had a publication bias as well.

## 5. CONCLUSION

If the overall effect size of the four insulin-resistance conditions, i.e., diabetes mellitus, PCOS, acromegaly, and obesity, is considered together, these conditions show a statistically significant role as the risk factors for AN. However, only T2DM appears to be a strong risk factor for AN when these conditions are analyzed separately. Although other conditions can also act as potential risk factors, we did not find any statistically significant association. Further studies should be conducted to determine the strength of association between insulin-resistance conditions and the development of AN.

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**Conflict of Interest**

The author declares that they have no conflict of interest.

**Data and materials availability**

All data associated with this study are present in the paper.

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