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**Permalink**

**Journal**

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**Publication Date**

**DOI**

Peer reviewed

# Depressive symptoms and multi-joint pain partially mediate the relationship between obesity and opioid use in people with knee osteoarthritis

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## SUMMARY

**Objectives:** To assess the relation of obesity to opioid use in people with or at risk of knee osteoarthritis (OA), and the extent to which this association is mediated by number of painful joints or depressive symptoms.

**Methods:** We used data from the Multicenter Osteoarthritis Study, a longitudinal cohort of older adults with or at risk of knee OA. Opioid use was identified by prescription medications and self-report. Obesity was defined as BMI $\geq$ 30 kg/m$^2$. Multi-joint pain was assessed using a

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standardized body homunculus, and depressive symptoms using the Center for Epidemiological Studies Depression scale. We quantified the direct and indirect effect of obesity on opioid use through the number of painful joints or depressive symptoms using causal mediation analysis by natural-effects models.

**Results:** We studied 2,335 participants (mean age: 68; mean BMI 31 kg/m$^2$; 60% women). Persons with obesity had ~50% higher odds of opioid use than those without. Estimates of indirect (mediated) effect by the number of painful joints and depressive symptoms suggested an increased odds of opioid use by 34% (odds ratio [OR] = 1.34, 95% CI: 1.04, 1.70) and 35% (OR 1.35, 95% CI: 1.05, 1.71), respectively, in obese vs non-obese individuals. The total effect of obesity on opioid use was higher in women than in men.

**Conclusions:** Multi-joint pain and depressive symptoms partially explained greater opioid use among obese persons with knee OA, demonstrating that the negative impact of obesity on knee OA extends beyond its influence on knee pain and structural progression.

## Keywords

Osteoarthritis (OA) as a diagnosis is a major driver for opioid prescriptions by primary care physicians for treating OA pain, despite guideline recommendations for the use of physical therapy and exercise as important management options[1–7]. Opioid prescription rates are even higher among those with OA who are obese than non-obese individuals[8,9,10]. Indeed, among obese individuals, OA is among the leading conditions for which opioids are prescribed. This trend is alarming given the well-recognized consequences of the opioid epidemic. Importantly, obesity is one of the strongest and most common modifiable risk factors for the development of OA and its progression[11,12] and understanding of the local and generalized effects that obesity can have on pain and joint structures has evolved in recent years[13]. While these effects have been noted across OA more broadly, they appear to be most significant for those with knee OA[14].

The reason obese individuals are more likely to be prescribed opioids hasn't been well-investigated to date. One potential explanation may be greater pain experienced by those who are obese. Obesity is thought to be a risk factor for chronic pain due to both increased joint loads and systemic inflammatory effects[15], contributing to the experience of pain in both weight-bearing and non-weight-bearing joints[14,16]. There is a dose-response relationship whereby individuals with greater body mass index (BMI) report greater rates of pain, ranging from 20% higher prevalence in the overweight to 254% in class III obesity than normal weight individuals[17,18]; and this effect is seen most prominently in those with knee OA[19].

Beyond pain prevalence itself, obesity may have other effects that could impact opioid prescription. Multi-joint pain, particularly in the lower extremities is a common experience in people with OA and who are obese[20,21]. Approximately 70% of people with OA report pain in, and seek treatment for, two or more painful joints[22]. In the Multicenter Osteoarthritis (MOST) Study, ~80% of those with bilateral knee pain, and ~64% of those

with unilateral knee pain had pain in other joints[23]. Similarly, a systematic review found a moderate and significant association between total body fat mass and the presence of multi-site or widespread musculoskeletal pain[24]. Previous work has reported that in people with knee OA, those with multi-joint pain are more likely to use opioids than those without multi-joint pain[25], but the sample was on average not obese. Thus current evidence indicates both pain and obesity are related to opioid use when evaluated independently, yet it remains unclear the degree to which pain could mediate the relationship between obesity and opioid use.

Apart from pain prevalence and multi-joint pain, an important comorbidity in people who are obese and among those with chronic pain that could impact opioid prescription is depression[26,27]. In obese individuals undergoing bariatric surgery, rates of comorbid depression range from 19 to 66%[28–30]. One quarter of people with pain report depression, and 4.4% of all adults report both depression and chronic pain[31]. Both obesity and pain share bidirectional associations with depression, indicating that either can be an antecedent or a consequence of depressive symptoms[32,33]. It has been demonstrated that depression is likely on the causal pathway in the obesity–pain relationship[32,34]. This would therefore suggest that depression may be on the pathway between obesity and opioid consumption through the impact of depression on pain.

Given the adverse consequences of opioid use, and that OA is one of the most common conditions for opioid prescriptions, greater understanding is needed of the increased prescribing of opioids. Such insights could potentially identify additional factors to manage that could lessen the risk of opioid use in people with knee OA who are obese. We therefore sought to evaluate the relation of obesity to opioid use and quantify the extent to which that association may be mediated by the number of painful joint sites or depressive symptoms in people with or at risk of knee OA.

## Methods

### Study sample

The MOST Study is a NIH-funded longitudinal study of 3,026 community dwelling adults between the ages of 50–79 years at enrollment who had or were at risk of developing knee OA, and were recruited from Birmingham, Alabama and Iowa City, Iowa from 2003 to 2005. Additional details of this cohort have been published elsewhere[35]. The study was approved by the institutional review boards at the University of Iowa, University of Alabama at Birmingham, University of California at San Francisco, and Boston University Medical Center[35]. We used data from the 60-month visit when detailed opioid use and prescriptions were obtained for these analyses.

### Measures

Obesity was assessed using the recognized standard of BMI cut-off $\geq$ 30 kg/m$^2$ and compared to those with BMI <30 kg/m$^2$. BMI was calculated from measurements for weight and height taken by a trained researched assistant. For multi-joint pain, participants completed a standardized body homunculus indicating the presence of painful joints in

the body, which were summed and this was exclusive of the affected knee. This method has been previously used and validated[36]. The presence of depressive symptoms was defined using the valid and reliable Center for Epidemiological Studies-Depression scale and the recommended cut score 16[37]. Our outcome was any opioid use categorized as Yes/No over the past 30 days based upon participants' reported medications which included documentation of all prescription medications, as well as a question specifically asking about use of a list of defined opioids and frequency. Specifically the following questions were asked: 'During the past 30 days, have you taken any of the following medications by mouth for joint pain or arthritis?' and 'During the past 30 days, have you taken any of the following stronger medications for joint pain or arthritis?' If 'yes' then they were asked the following 'How often do you take any of these medications for joint pain or arthritis?' Potential confounders included age, sex, race, geographic site, and the Charlson comorbidity index[38].

### Analysis

We assessed the potential mediating roles of number of painful joint sites and depressive symptoms on the effect of obesity on opioid use by causal mediation analyses[39,40]. We expressed the extent of these potential mediating effects by estimating the natural indirect (i.e., mediated) effect as well as the remaining natural direct effects, which were not mediated by these factors, to quantify the total effect of obesity on opioid use (Fig. 1). We additionally assessed whether the indirect effects of obesity on opioid use were different between men and women. The natural-effect models[41] for assessing the mediating roles of number of painful joints and depressive symptoms included the potential confounders listed above, whereas the sex-specific natural-effect models were adjusted for age, race, geographic site, and comorbidities. Finally, we conducted a sensitivity analysis with similar models to determine if frequency of opioid use resulted in different effect estimates. Opioid use was dichotomized into frequent use ( 3 times/week) vs sometimes ( 2 times/week). All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

**Results:** There were 2,335 eligible subjects (mean age: 68; mean BMI 31 kg/m$^2$; 60% women) Table I.

Overall the percentage of opioid users was ~14% or (325/2,335). The percentage using opioids was generally greater in those with obesity than those who were not obese, and generally increased with greater number of painful joints (Table II). Among those without depressive symptoms, opioid use in those with obesity was greater than those who were not obese; no difference was noted in prevalence of opioid use by obesity status among those with depressive symptoms (Table III).

### Total effect of BMI on opioid use

The total effect of obesity on opioid use (i.e., that includes both indirect and direct effects) was similar in the model evaluating number of painful joint sites (OR = 1.55, 95% CI: 1.20, 1.98) and in the one evaluating depressive symptoms (OR = 1.47, 95% CI: 1.14, 1.89) (Table IV).

## Mediation analysis

Estimates of the natural indirect effect indicated that the odds of opioid use for persons with obesity compared with non-obese individuals, was 34% and 35% higher, due to mediation by the number of painful joints (indirect effect odds ratio [OR] = 1.34, 95% bootstrap CI: 1.04, 1.70) and depressive symptoms (indirect effect OR = 1.35, 95% bootstrap CI: 1.05, 1.71), respectively (Table IV). Effect estimates of the sex-stratified mediation analysis appeared slightly higher for obese women compared to obese men for the mediating effects by the number of painful joint sites or depressive symptoms on the association of obesity and opioid use (Table IV). However due to wide overlapping confidence intervals, the comparison is inconclusive.

## Sensitivity analyses

When considering frequency of opioid use as the outcome, we compared those using opioids frequently to those using opioids sometimes. The total effect of obesity on frequent vs sometime opioid use was (OR 1.17, 95% CI 0.82, 1.64), for the number of painful joints model and in the depressive symptoms model was (OR 1.13, 95% CI 0.79, 1.59), which were somewhat lower than the associations in the primary analyses. The direct effects indicated 17% and 12% higher odds of opioid frequent use compared to those who used opioids sometimes in both analyses, respectively (Table V). In contrast to the primary analyses, there was no mediating effects of painful joints (OR = 1.00, 95% CI: 0.71,1.39) or depressive symptoms (OR = 1.00, 95% CI: 0.72, 1.39) in the relation of obesity to frequent opioid use compared with use of opioid sometimes. Effect estimates were higher in women compared with men, though the sex-specific effects were of lower magnitude than noted in the primary analyses though again with overlapping confidence intervals, and were close to the null for men (Table V).

# Discussion

We quantified the extent of the association between obesity and opioid use, encompassing findings to a large sample with or at risk of knee OA. Our findings of multi-joint pain and depressive symptoms as mediators of the effect of obesity on opioid use provides insight as to why individuals with or at risk of knee OA who are obese may be receiving greater prescription of opioids than non-obese individuals[42]. We found that people with or at risk of knee OA who are also obese have higher prevalence of multi-joint pain compared with those who are not obese.

Among people with OA, pain is the main driver of seeking out healthcare assistance for symptom management. Our results suggest that the common experience of multi-joint pain in people with OA, which we and others have observed to be worse in those with obesity[21], is a potential reason why these individuals may seek or receive more opioids compared with non-obese individuals. Those with multi-joint pain who are non-obese also use analgesics and opioids more than those with single joint pain, and experience greater pain severity[43,44]. Considering that increased opioid use is seen with both obesity and multi-joint pain, it is not surprising that the latter would mediate the former. However, as our study is cross-sectional, we cannot confirm directionality.

We also found depressive symptoms to mediate the relationship between obesity and opioid use. Treatment for either obesity or depression can improve the other[32]. For example, duloxetine, an antidepressant, has been shown to be more cost-effective for pain intensity than usual care such as intra-articular injections, opioids, and total knee replacement (TKR)[45]. Such findings provide additional support for screening of depressive symptoms in people with knee OA who are obese, as addressing depressive symptoms may also help with weight management. Improvement in either weight or depressive symptoms would likely help reduce pain and may potentially forego the consideration of opioids. Importantly, chronic opioid use may lead to clinical depression[46] and therefore should be avoided in individuals with depressive symptoms.

The results of our sex-stratified are inconclusive. We are unaware of studies showing sex differences in opioid use in individuals who are obese. In non-obese samples, existing literature reports that women are typically more likely to be prescribed and use opioids than men[47,48]. This is in line with women experiencing more chronic pain, thought to be largely due to physiological, hormonal and psychosocial factors[49]. Data from a large multi-payer database in the United States demonstrated that 59% of opioid users were female and BMI associations with opioid use was stronger in women (RR, 1.43; 95% CI, 1.40–1.46) than in men (RR, 1.15; 95% CI, 1.12–1.19)[8]. Given the high rates of opioid prescriptions for people with OA[50] that are further elevated for those who are obese[8], greater understanding of differences by sex is needed to enable appropriate approaches to management.

In our sensitivity analyses assessing the impact of obesity on the frequency of opioid use, the increased risk for more frequent use of opioids was less than half of that found in our main analysis where opioid use was treated as present or absent. We found no mediating effect of either painful joints or depressive symptoms for the relation of obesity on frequent opioid use compared with opioid use that occurred sometimes. This suggests that in those who are obese, with either multiple painful joints or depressive symptoms, the risk of using opioids is greater overall and has less influence on the frequency of consumption. These initial findings are important for clinicians as our results suggest that in obese individuals with either multi-joint pain or depressive symptoms, the latter two provide treatment targets for pain management to be explored prior to opioid prescription, though their presence may not affect frequency of opioid use beyond "any use" of opioids. Given that this is the first exploration of frequency of opioid use as an outcome in this mediation analysis of obesity by depressive symptoms and number of painful joints, further studies are needed to corroborate our findings.

Limitations to our study include that we did not account for pain severity. Although we found a mediating effect of depressive symptoms and multi-joint pain on the association between obesity and opioid use, our analysis was cross-sectional and therefore the possibility of reverse causation needs further investigation in a longitudinal study. Our questions regarding the use of opioids were limited to their use for joint pain/arthritis. It is possible that participants were taking opioids for a different reason that we did not capture and are therefore unable to know the effect of. Due to inadequate numbers, we were unable to assess the association of those who were underweight with opioid use. As with observational studies generally, residual confounding remains possible. Strengths of our

study include a large community-based sample, the use of modern causal inference-based approaches to mediation analysis to provide insight into reasons why individuals with or at risk of knee OA who are obese may be receiving greater prescription of opioids than non-obese individuals and a sensitivity analysis looking at frequency of opioid use as an outcome.

Our findings should be considered in the context of current management practices and evidence-based treatment guidelines. Our results, along with other analyses of large databases in the US, suggest that people who are obese and have joint pain, are being prescribed opioids more than non-obese people[8,10], while others have shown that in people with knee OA, opioids are being prescribed at approximately twice the rate of guideline endorsed physical therapy or lifestyle counselling[1]. Current guidelines for knee OA conditionally recommend[6], or recommend against[3,6] the use of opioids for pain management and heavily focus on active strategies such as education, exercise, mind-body therapies and weight management as necessary[3,6]. Of particular interest given the results of our study, are the recommendations by OARSI for individuals with widespread pain (i.e., multi-joint pain) and/or depression, which includes cognitive behavioral therapy, aquatic exercise, self-management or pain management programs along with duloxetine to address mood and chronic pain[3].

Possible explanations for deviation from guideline-based care for those with obesity compared with those who are not obese may be related to physician or patient factors. Historically, studies have reported that there is explicit and implicit stigma in physicians' views of patients who are obese, influencing patient–provider interactions and the quality of care offered[51]. On the one hand, individuals who are obese are assumed to be more likely to be non-adherent, and have to deal with less frequent prescribing of medication[51]. For example, a systematic review of adherence to lifestyle interventions for obesity indicates reduced effectiveness due to poor attendance and adherence rates, which may in turn be impacted by greater movement related pain[52]. However, the greater prescription of opioids among those who are obese compared with those who are not obese negates concerns of undertreatment, and in fact, may reflect overtreatment instead[53]. Another potential explanation for the increased rate of opioid prescriptions could be due to patient preference for medication over active interventions such as physical therapy; whether preferences differ by an individual's obesity status it not known.

Lastly, our findings provide additional support for clinicians to focus on the important comorbidities of multi-joint pain and depressive symptoms, particularly in individuals with obesity, to enable utilization of recommended management options and thereby minimize use of opioids. A multifactorial approach to pain management is important since chronic pain, a common experience with knee OA and obesity, is a risk factor for increased opioid use[54]. Early referral to physical therapy for pain management decreases the risk of a first-time opioid prescription[55–57], and engagement in a structured exercise and education program reduces opioid and analgesic use[58]. Clinicians could also consider the role of screening for and addressing depressive symptoms as part of a comprehensive approach to pain management. Such approaches may be useful as a means of limiting opioid use. Consideration of appropriate management options are urgently needed, given that OA is one

of the most frequent conditions for which opioids are being prescribed for people who are obese in the US compared with other painful conditions.[8]

## Conclusions

In people with or at-risk for knee OA, who are obese, the number of painful joints and depressive symptoms partially explain the association between obesity and opioid use. Both multiple painful joints and depressive symptoms can increase pain severity through multiple mechanisms including mechanical load, inflammation and psychosocial influences. These effects may disproportionately affect people who are obese, which is itself a major risk factor for knee OA and its progression, and is associated with greater opioid use. Greater efforts are needed to mitigate opioid prescribing in OA which is a major driver for opioid prescribing in the US. Updated OA treatment guidelines provide guidance on efficacious treatments that may help avoid the known negative consequences of opioid use.

## Funding source

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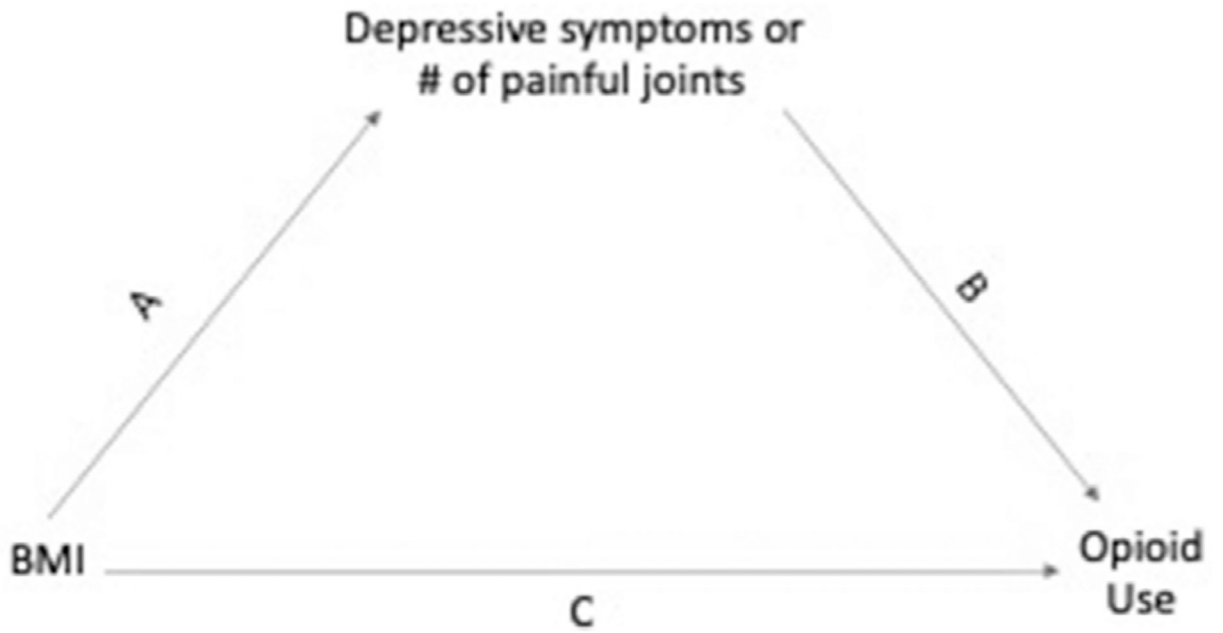
**Fig. 1. Directed acyclic graph**

Indirect effect of BMI on opioid use mediated by depressive symptoms or # of painful joints
= A + B

Direct effect of BMI on opioid use = C

Total effect of BMI on opioid use = A + B + C.

**Table I**

Participant characteristics N = 2,335

| | |
|---|---|
| Age, years mean (SD) | 67.8 (7.8) |
| Women n (%) | 1,411 (60.4) |
| BMI, 30 kg m$^2$, n (%) | 1,155 (49.6) |
| CES-D 16, n (%) | 269 (11.5) |
| Number of Comorbidities [*], mean (SD) | 0.52 (0.98) |
| Race – white n (%) | 1967 (84) |
| Study Site – UAB n (%) | 1,135 (49) |

[*] Missing data n = 13 (<1%).

**Table II**

Percentage of opioid use by number of pain sites and BMI level

| # of Pain sites | <30 kg/m$^2$ n = 1,173 | 30 kg/m$^2$ n = 1,155 |
|---|---|---|
| 0 | 1/150 (0.7%) | 2/115 (1.7%) |
| 1–2 | 12/289 (4.2%) | 17/225 (7.6%) |
| 3–5 | 35/322 (10.9%) | 31/323 (9.6%) |
| 6–10 | 53/292 (10.9%) | 77/304 (25.3%) |
| 11+ | 32/118 (27.1%) | 62/184 (33.7%) |

**Table III**

Percentage of opioid use by depressive symptoms and BMI level

| Depressive symptoms | <30 kg/m² n = 1,173 | 30 kg/m² n = 1,155 |
|---|---|---|
| CES-D <16, n (%) | 94/1,056 (8.9%) | 138/1,003 (13.7%) |
| CES-D 16, n (%) | 40/117 (34.1%) | 51/152 (33.6%) |

**Table IV**

Association of obesity with opioid use – direct, indirect and total effects

| BMI in kg/m² | Opioid use mediated by # of painful joints | | |
|---|---|---|---|
| | *Whole sample N = 2,322 | †Stratified model | |
| | | Female n = 1,405 | Male N = 917 |
| <30 | 1.0 | 1.0 | 1.0 |
| 30 | D - 1.16 (1.08, 1.25) | D - 1.17 (1.07, 1.28) | D - 1.15 (1.00, 1.31) |
| | I – 1.34 (1.04, 1.70) | I – 1.40 (0.98, 1.32) | I – 1.20 (0.76, 1.87) |
| | T – 1.55 (1.20, 1.98) | T – 1.64 (0.79, 2.25) | T – 1.37 (0.87, 2.14) |
| | Opioid use mediated by depressive symptoms | | |
| | *Whole sample N = 2,328 | †Stratified model | |
| | | Female N = 1,407 | Male N = 921 |
| <30 | 1.0 | 1.0 | 1.0 |
| 30 | D - 1.09 (1.03, 1.16) | D – 1.10 (1.03, 1.18) | D - 1.08 (0.96, 1.24) |
| | I – 1.35 (1.05, 1.71) | I – 1.43 (1.07, 1.90) | I – 1.18 (0.75, 1.84) |
| | T – 1.47 (1.14, 1.89) | T – 1.57 (1.15, 2.13) | T – 1.28 (0.82, 1.99) |

* Adjusted for age, sex, race & geographic location, comorbidities.

† Adjusted for same potential confounders except for sex D-direct effects, I- indirect effects, T – total effects.

**Table V**

Association of obesity with frequent vs sometimes opioid use – direct, indirect and total effects

| BMI in kg/m² | Frequency of opioid use (frequently vs sometimes) mediated by # of painful joints | | |
|---|---|---|---|
| | *Whole sample | †Stratified model | |
| | | Female | Male |
| <30 | 1.0 | 1.0 | 1.0 |
| 30 | D - 1.17 (1.07, 1.27) | D - 1.18 (1.06, 1.30) | D - 1.12 (0.93, 1.41) |
| | I – 1.00 (0.71, 1.39) | I - 1.07 (0.72, 1.59) | I – 0.85 (0.43, 1.69) |
| | T – 1.17 (0.82, 1.64) | T - 1.26 (0.83, 1.91) | T – 0.95 (0.48, 1.92) |

| BMI in kg/m² | Frequency of opioid use (frequently vs sometimes) mediated by depressive symptoms | | |
|---|---|---|---|
| | *Whole sample | †Stratified model | |
| | | Female | Male |
| <30 | 1.0 | 1.0 | 1.0 |
| >30 | D - 1.12 (1.02, 1.23) | D - 1.12 (1.01, 1.24) | D - 1.11 (0.89, 1.41) |
| | I – 1.00 0.72, 1.39) | I - 1.11 (0.76, 1.61) | I – 0.81 (0.40, 1.63) |
| | T – 1.13 (0.79, 1.59) | T - 1.24 (0.81, 1.89) | T – 0.90 (0.46, 1.77) |

* Adjusted for age, sex, race & geographic location, comorbidities.

† Adjusted for same potential confounders except for sex D-direct effects, I- indirect effects, T – total effects.