


## SHORT COMMUNICATION

# Obesity a predictor of outcomes of COVID-19 hospitalized patients—A systematic review and meta-analysis

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## Abstract

Coronavirus disease 2019 (COVID-19) pandemic is a global health crisis. Very few studies have reported association between obesity and severity of COVID-19. In this meta-analysis, we assessed the association of obesity and outcomes in COVID-19 hospitalized patients. Data from observational studies describing the obesity or body mass index and outcomes of COVID-19 hospitalized patients from December 1, 2019, to August 15, 2020, was extracted following PRISMA guidelines with a consensus of two independent reviewers. Adverse outcomes defined as intensive care units, oxygen saturation less than 90%, invasive mechanical ventilation, severe disease, and in-hospital mortality. The odds ratio (OR) and 95% confidence interval (95% CI) were obtained and forest plots were created using random-effects models. A total of 10 studies with 10,233 confirmed COVID-19 patients were included. The overall prevalence of obesity in our study was 33.9% (3473/10,233). In meta-analysis, COVID-19 patient with obesity had higher odds of poor outcomes compared with better outcomes with a pooled OR of 1.88 (95% CI: 1.25–2.80;  $p = 0.002$ ), with 86% heterogeneity between studies ( $p < 0.00001$ ). Our study suggests a significant association between obesity and COVID-19 severity and poor outcomes. Our results findings may have important suggestions for the clinical management and future research of obesity and COVID-19.

## KEYWORDS

2019-nCoV, body mass index (BMI), coronavirus disease, COVID-19, mechanical ventilation, mortality, obesity, SARS-CoV-2, severe acute respiratory syndrome

## 1 | INTRODUCTION

As of August 20, 2020, a total of 23 million coronavirus disease 2019 (COVID-19) cases have been reported, leading to 814,797 deaths worldwide.<sup>1</sup> This pandemic has posed a greater risk to population and healthcare. Research studies have shown that COVID-19 not only

affects the respiratory system but affects multiple organs of the body.<sup>2–5</sup> In addition, certain groups of people, including the elderly and immunocompromised, have been identified as most susceptible to the virus, especially those with underlying diseases like diabetes, hypertension, cardiovascular disease etc.<sup>6</sup> Researchers across the globe have been exploring predictors of severity of COVID-19 cases to identify and

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stratify them accordingly. More recent studies are focusing on identifying other high-risk patients helping in their early management.<sup>7</sup>

According to recent trends observed in the United States from 1999 to 2000 through 2017–2018, the age-adjusted prevalence of obesity increased from 30.5% to 42.4%.<sup>8</sup> Obesity, a subclinical inflammatory state caused by an excess of inflammatory cells in adipose tissue, is known to be a risk factor for various disease states.<sup>9,10</sup> The majority of people who had high mortality due to COVID-19 have suffered from other comorbidities, the most prevalent being cardiovascular disease, hypertension, and respiratory diseases, all of these are also strongly associated with obesity.<sup>11–13</sup> A lot of our current knowledge about the relationship between obesity and COVID-19 has come from previous evidences, showing that morbidly obese patients had increased risk of hospitalization, mechanical ventilation, and mortality during the H1N1 pandemic and seasonal influenza.<sup>14–16</sup> In addition, it has been noted that influenza A, along with several other pathogens, uses adipose tissue as a viral reservoir.<sup>17</sup> Obese patients, along with a weakened immune system may provide a virus with a larger replication region.

A few recent articles have begun to explore the relationship between obesity and COVID-19, but are limited in sample size and geographical locations. Hence, the aim of our meta-analysis is to assess the effect of obesity on outcomes in the COVID-19 hospitalizations.

## 2 | METHODS

### 2.1 | Endpoint

The aim of the study is to evaluate the association between obesity and outcomes in confirmed COVID-19 positive hospitalized patients. COVID-19 confirmation was evaluated by combined findings of reverse transcription-polymerase chain reaction, serology, symptoms, and magnetic resonance imaging chest in majority of those studies.

Obesity defined as body mass index (BMI)  $\geq 25$  or 28 or 30 or confirmed obesity comorbidity in individual studies. Composite poor outcomes were defined by intensive care unit (ICU) admission, oxygen saturation less than 90%, invasive mechanical ventilation (IMV) utilization, severe disease, and in-hospital mortality.

### 2.2 | Search strategy and selection criteria

A systematic search was conducted on published studies using PRISMA guidelines<sup>18</sup> and followed the MOOSE checklist<sup>19</sup> from December 1, 2019 to August 15, 2020. We searched PubMed, Web of Science, Scopus, and medRxiv for observational studies that described BMI or comorbidities and outcomes of COVID-19 patients following keyword or MESH terms: COVID-19 or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or 2019-novel coronavirus. Studies were included in this meta-analysis if they had higher BMI or comorbid obesity and outcomes of COVID-19 hospitalized patients. Literature other than observational studies, non-English literature, non-full text, and animal studies were excluded.

Flow diagram of the literature search and study selection process is described in Figure 1.

### 2.3 | Study selection

Abstracts were reviewed, and articles were retrieved and reviewed for availability of data on Obesity or BMI and outcomes of COVID-19 patients. Studies which gave details on outcomes were selected for quantitative analysis. Preeti Malik and Urvis Patel independently screened all identified studies and assessed full-texts to decide eligibility. Any disagreement was resolved through consensus.

### 2.4 | Data collection

From the included studies, we extracted the following variables higher BMI, obesity, and outcomes. Details on binary outcomes like ICU versus non-ICU admission, severe versus non-severe disease, IMV versus no-IMV use, oxygen saturation less than 90% versus greater than 90%, in-hospital mortality versus discharged alive and survivors were collected using prespecified data collection forms by two authors (Preeti Malik and Urvis Patel) with a common consensus.

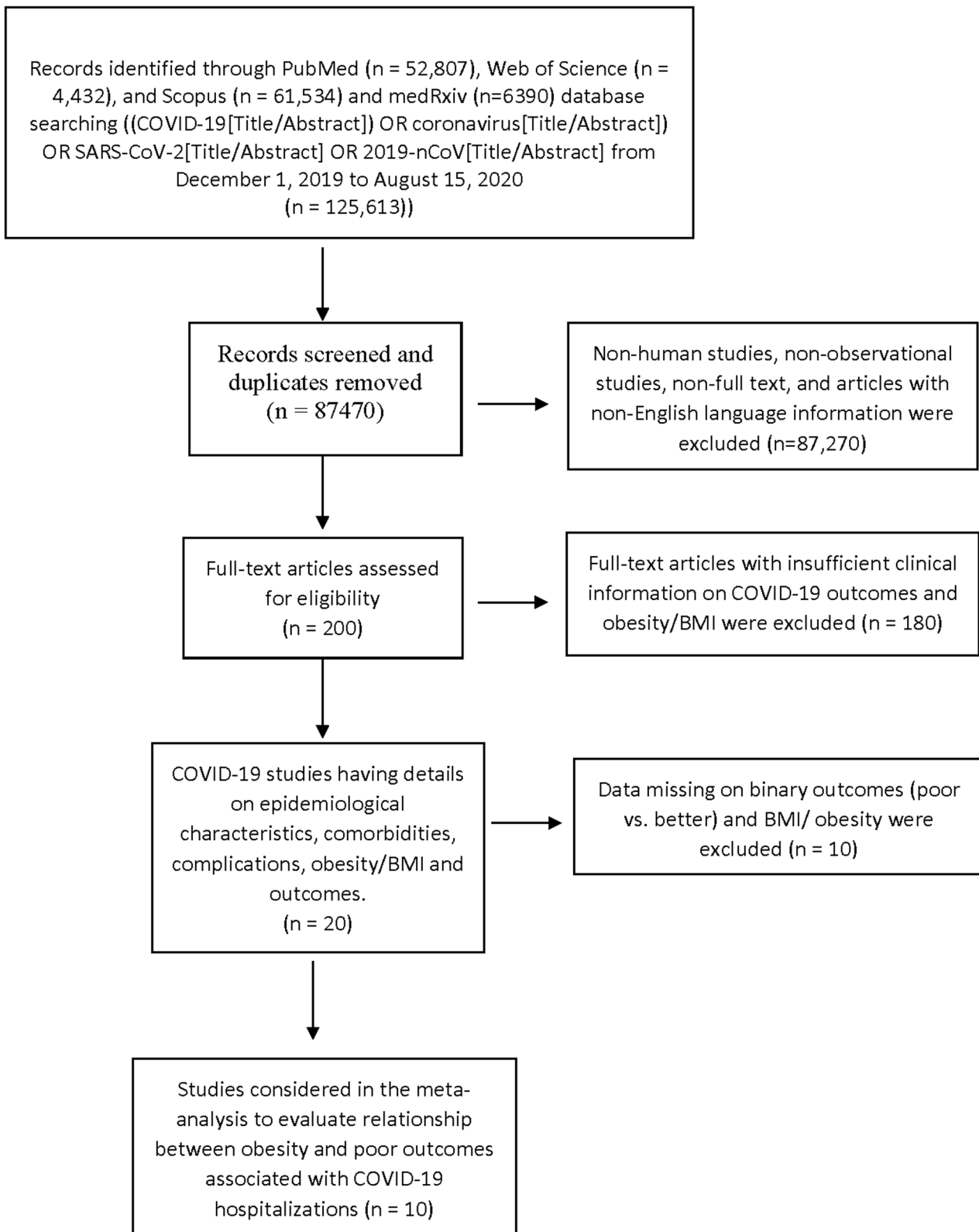
We have presented the study characteristics like the first author's last name, publication month and year, country of origin, sample size, study design mean or median age, sex, outcomes and definition of obesity assessed in that individual study Table 1.

### 2.5 | Statistical analysis

Data analysis was performed using Review Manager version 5.4 (The Nordic Cochrane Center, The Cochrane Collaboration). The Maentel-Haenszel formula was used to calculate dichotomous variables to obtain odds ratios (ORs) along with its 95% confidence intervals (95% CI) to describe the relationship of obesity and outcomes of COVID-19 patients in each study. Random-effects models were used regardless of heterogeneity to estimate the combined effect and its precision, to give a more conservative estimate of the ORs and 95% CI.  $p < 0.05$  was considered significant. The  $I^2$  statistic was used to assess statistical heterogeneity and value greater than 75% was considered significant heterogeneity. The Newcastle–Ottawa scale was used to assess the quality of the included studies<sup>20</sup> (File S1.2). Sensitivity analysis was performed to assess the effect of publication bias and heterogeneity by excluding outlying studies on the funnel plot.

## 3 | RESULTS

In our literature search 200 full text articles were assessed for eligibility. After considering eligibility criteria, we included 10 observational studies with 10,233 confirmed cases of COVID-19 patients detailing obesity or high BMI and outcomes. The overall



**FIGURE 1** Flow diagram of literature search and study selection process of coronavirus disease 2019 (COVID-19) outcomes and obesity

prevalence of obesity was 33.9% (3473/10,233) and in patients with poor outcomes, the obesity prevalence was 37.6% (1303/3459).

Meta-analysis of all 10 studies showed that COVID-19 patient with pre-existing obesity or high BMI had higher odds of poor

outcomes compared to better outcomes with a pooled OR of 1.88 (95% CI: 1.25–2.80;  $p = .002$ ), and 89% heterogeneity between studies ( $p \leq .00001$ ) (Figure 2). Sensitivity analysis was conducted by eliminating the four outlying studies (Mikami et al., Deng et al.,

**TABLE 1** Study characteristics, outcomes, and obesity or BMI

Study	Country	Sample size (n)	Study design	Mean or median age	Male	Outcomes	Obesity or body mass index (BMI) in kg/m <sup>2</sup>
Paranjpe et al.	USA	1078	Retrospective multi-center	65	627	In-hospital mortality versus discharged alive	In hospital mortality: BMI median = 32 Discharged alive BMI median = 28
Goyal et al.	USA	393	Retrospective multi-center	62	238	Invasive mechanical ventilation versus no invasive mechanical ventilation	Obesity was defined as BMI ≥ 30
Huang et al.	China	202	Retrospective multi-center	44	116	Severe versus non-severe <sup>a</sup>	BMI ≥ 28
Mikami et al.	USA	6493	Retrospective multi-center	62 (survivor), 76 (non-survivor)	1611	Non survivors versus survivors	Comorbidity obesity
Deng et al.	China	65	Retrospective single-center	32.5 (severe + critical), 35 (moderate)	36	Severe + critical versus moderate <sup>a</sup>	BMI ≥ 28
Marcello et al.	USA	13442	Retrospective multi-center	53	7481	Died versus discharged	BMI ≥ 30
Suleyman et al.	USA	463	Retrospective single-center	57.5	204	Hospitalized versus discharged	Any obesity and severe obesity as BMI > 40
Claudia et al.	Switzerland	99	Retrospective single-center	67	62	Severe versus non-severe <sup>b</sup>	BMI > 30
Zhang et al.	China	788	Retrospective single-center	(Severe + critical) versus mild <sup>b</sup>	407	(Severe + critical) versus mild <sup>a</sup>	BMI > 25
Ferguson et al.	USA	72	Retrospective multi-center	60.4	38	ICU versus non-ICU	BMI > 30
Total		23,095					

Note: The sample size is total COVID-19 confirmed patients included in that individual study. References of the studies included in analysis are in supplemental file 1.3.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; ICU, intensive care unit.

<sup>a</sup>World Health Organization and the National Health Commission of China interim guidelines defined disease severity and improvement as follows: mild cases: the mild clinical symptoms and no pneumonia in imaging. Moderate cases: symptoms like fever and respiratory tract symptoms, etc, and pneumonia can be seen in imaging. Severe cases: meeting any of the following—respiratory distress, respiratory rate ≥30 breaths/min; SpO<sub>2</sub> ≤93% at rest; and PaO<sub>2</sub>/FIO<sub>2</sub> ≤300. Patients with greater than 50% lesion progression within 24 to 48 h. Critical or extremely severe cases: if they have one of the following: respiratory failure requiring mechanical ventilation, shock, and other organ failure requiring ICU treatment.

<sup>b</sup>Severe COVID-19 progression defined as a composite of transfer to ICU during the index hospital stay and all-cause in-hospital mortality, both verified by chart review. The sample size is total COVID-19 confirmed patients included in that individual study.

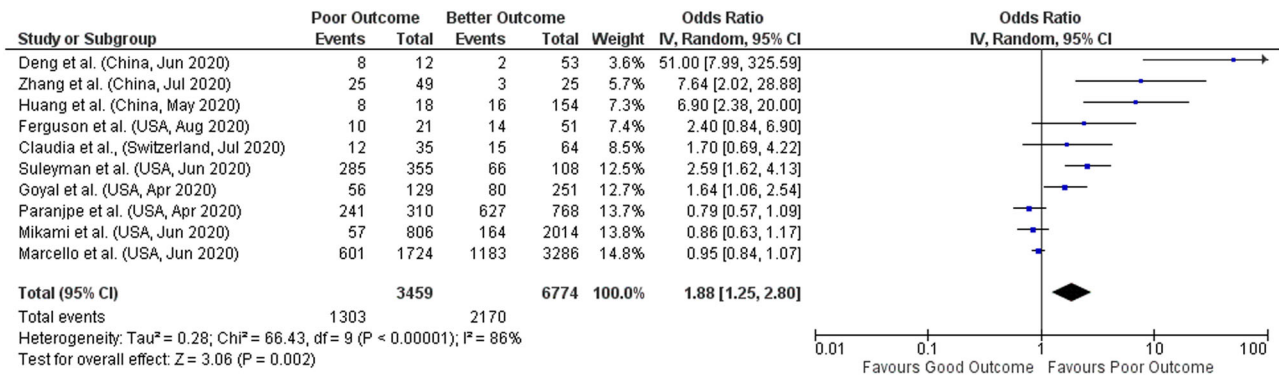
Marcello et al., and Paranjpe et al.,) on funnel plot (File S1.1) to account for heterogeneity. Results after sensitivity analysis also showed significant pooled-OR of 2.63 (95% CI: 1.68–4.11;  $p < .00001$ ) with 51% heterogeneity between studies ( $p = .07$ ).

## 4 | DISCUSSION

Our meta-analysis found 37.6% prevalence of pre-existing obesity in COVID-19 patients with poor outcomes. Another main finding of our meta-analysis was, COVID-19 patients with pre-existing obesity had 1.88-folds higher risk of having worse outcomes. Our results fall in line with previous studies that have documented an above normal BMI as

a potential risk factor for the coronavirus.<sup>7,10</sup> Although the reasons behind the relationship between obesity and COVID-19 still remain unclear, there have been several studies that have proposed various underlying mechanisms that may provide us with some insight.<sup>7,9,21</sup>

One plausible theory is that, SARS-CoV-2 binds to the ACE2 receptor in the cellular membrane and once inside a host cell it slows down angiotensin II metabolism leading to an increased expression of angiotensin II. Angiotensin II leads to pulmonary vasoconstriction and acute lung injuries, two of the prominent symptoms of COVID-19. Since obese patients have more adipose tissue, they have more ACE2 receptors providing the virus with more entry points into a host cell. In addition, obesity is strongly associated with Type 2 diabetes (T2DM) which also leads to an increase in ACE2 receptors. In people with T2DM,



**FIGURE 2** Forest plot of obesity and outcome in COVID-19 hospitalized patients. COVID-19, coronavirus disease 2019

angiotensin II levels are positively correlated with body weight. As a result, if an obese patient with a comorbid of T2DM becomes infected with the SARS-CoV-2, their previously high angiotensin II levels will further elevate leading to greater complications.<sup>7</sup>

In the RAS pathway, a precursor protein Agt is secreted from various tissues (including adipose tissue) and then is cleaved twice by the enzymes renin and ACE resulting in the production of angiotensin II. Another mechanism is, in obese people there is both overexpression of Agt and an overactivation of the RAS system in adipose tissue resulting in an increased production of angiotensin II.<sup>21</sup> This coupled with the increase of angiotensin II due to COVID-19 may lead to poorer outcomes for obese patients.

Furthermore, obesity has been known to compromise the adaptive and innate immune system responses. In obesity there is reduced macrophage activation, increased proinflammatory cytokine production, and impaired B and T cell activation.<sup>9</sup> As a result, an obese patient is not only more susceptible to being infected with SARS-CoV-2 but also cannot fight the infection leading to increased morbidity in COVID-19 infections. Moreover, obesity not only causes a wide array of organ and immune system dysfunction, but also makes it more difficult to evaluate and treat patients in a clinical setting. Because COVID-19 causes severe respiratory complications including acute respiratory distress syndrome, many patients who contract the virus may need mechanical ventilation. Ventilating obese patients is quite challenging due to decreased diaphragmatic excursion, decreased expiratory reserve volume, and decreased lung functional capacity.<sup>7</sup> Besides, many hospitals are not well equipped to easily evaluate and treat obese patients.

There is increasing prevalence of obesity in the US population<sup>8</sup> and 8 out of 10 studies in our meta-analysis were conducted in US population. However, this high prevalence of obesity is really important to be considered worldwide since the association of obesity and severity of COVID-19 has been reported and it is a major public health problem worldwide and so is the SARS-CoV-2 infection. Considering our results and severity of COVID-19 and the proposed mechanisms and pathology in the literature, it is suggested that patients with obesity are at higher risk of COVID-19 and poor

outcomes. Hence, there is need for increased surveillance, priority on early detection and testing, and aggressive therapy for patients with obesity and COVID-19 infections.

#### 4.1 | Strengths, limitations, and future directions

The main limitation of this meta-analysis is the heterogeneity of the included studies. All the studies are retrospective studies due to the lack of data from prospective studies and randomized trials. Furthermore, the different definitions of the severity of the COVID-19 disease and discrepancy in the cut off values for the BMI and different diagnostic criteria for obesity might be explanations for the heterogeneity. Another limitation is that, the studies included in our analysis have not performed multivariate analysis to find association between obesity and severity of COVID-19 adjusting for diabetes and/or hypertension and/or cardiovascular disease. Despite these limitations, our meta-analysis of 10,233 confirmed COVID-19 patients suggests that obesity plays a significant role in the progression of COVID-19. This may help in early triage of high-risk patients and prevent the complications associated with poor outcomes by early and aggressive management of such patients.

## 5 | CONCLUSION

Our meta-analysis suggests that obesity is significantly associated with poor outcomes in COVID-19 patients. Obesity has added additional burden on both the patient and healthcare, resulting in an overall poorer prognosis. Additionally, obesity negatively impacts the body in many ways from weakening the immune system to over activating various pathways resulting in an overall increased morbidity. More studies on obesity and COVID-19 should be designed to evaluate the effect of the obesity epidemic on coronavirus pandemic.

#### CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Conceptualization: Preeti Malik; methodology: Preeti Malik and Urvis Patel; acquisition of data: Preeti Malik and Urvis Patel; formal analysis and investigation: Preeti Malik; writing original draft preparation: Preeti Malik, Urvis Patel, Karan Patel, Mehwish Martin, Deep Mehta, and Chail Shah; writing review, critical feedback, and editing: Ashish Sharma and Faizan Ahmad Malik; funding acquisition: none; resources: Ashish Sharma; supervision: Ashish Sharma.

## ETHICAL STATEMENT

Though this article does not contain any studies with direct involvement of human participants or animals performed by any of the authors, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## INFORMED CONSENT

The data used in this study is deidentified and collected from the studies published online thus informed consent or IRB approval was not needed for this study.

## DATA AVAILABILITY STATEMENT

The data is collected from the studies published online, publicly available, and specific details related to data and/or analysis will be made available upon request.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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