Limited contribution of insulin resistance and metabolic parameters to obesity-associated increases in ambulatory blood pressure in a black African community☆

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ABSTRACT

Although accounting for a striking proportion of obesity effects on blood pressure (BP) in other populations, the extent to which obesity-associated increases in BP are explained by insulin resistance and metabolic changes in populations of African ancestry is uncertain. We determined the contribution of insulin resistance and associated metabolic abnormalities to variations in office or ambulatory BP in a black African community with prevalent obesity and hypertension. In 1225 randomly selected participants of black South African ancestry (age > 16 years, 43.1% obese, 47.4% abdominal obesity), we assessed adiposity indexes, the homeostasis model of insulin resistance (HOMA-IR) and associated metabolic abnormalities and office or ambulatory (n = 798) BP. In separate models, waist circumference (p < 0.0005–< 0.0001) and HOMA-IR (p < 0.51–0.005), were independently associated with office, 24 h, day or night systolic (SBP) or diastolic (DBP) BP. However, whilst a one standard deviation increase in waist circumference translated into a 1.47–3.08 mm Hg increased in office, 24-h SBP or DBP, in mediation analysis HOMA-IR accounted for only 0.12–0.30 mm Hg of the impact of a one standard deviation effect of waist circumference on office, and 24-h SBP and 0.003–0.17 mm Hg of the impact of a one standard deviation effect of waist circumference on office and 24-h DBP. In conclusion, in a black African community, insulin resistance accounts for a negligible proportion of the impact of obesity on office or ambulatory BP.

1. Introduction

A steady rise in the global prevalence of obesity has been observed [1, 2] with one-third of adults in the United States [3], and a similar proportion of adult women in developing countries such as South Africa [4] being obese. Substantial evidence favours a cause-effect relationship between obesity and hypertension [5], including a meta-analysis of 136 studies demonstrating resolution of hypertension in 61.7% of patients following bariatric surgery [6]. As recently reviewed, additional meta-analyses have reported a resolution of hypertension in 50%–83.4% of patients following bariatric surgery [7]. Several mechanisms have been proposed to explain the impact of obesity on blood pressure (BP) including activation of the sympathetic nervous [5,8,9] or renin-angiotensin-aldosterone [5,8,10,11] systems and through renal effects on sodium retention [5,8]. Central to a number of the mechanisms that explain obesity-induced hypertension is insulin resistance [5,8] a change thought to provide a simple index of obesity effects on BP and hence a potential primary target for ameliorating obesity associated effects on BP.

Insulin resistance or associated increases in insulin concentrations...
may contribute to an enhanced sympathetic nervous system activation and subsequently stimulate renin release [5,8]. Moreover, insulin resistance or the consequent hyperinsulinemia increase renal sodium reabsorption [5,8]. Thus, several obesity-associated metabolic abnormalities indexing insulin resistance, including the homeostasis model of insulin resistance (HOMA-IR), are independently associated with BP [12–14].

The central role of insulin resistance or associated metabolic changes in mediating obesity-associated increases in BP is supported by large population-based studies demonstrating that these metabolic abnormalities may mediate a total of 68% of obesity-associated office or clinic BP effects [13]. Thus, targeting the metabolic abnormalities associated with obesity could manage a significant proportion of the effects of obesity on office or clinic BP. However, whether insulin resistance and related metabolic abnormalities explain a similar proportion of the impact of obesity on BP in those of black African ancestry is unknown. In this regard, previous small studies conducted in a black African community have failed to demonstrate an independent relationship between HOMA-IR and ambulatory BP [15], despite an independent relationship between central obesity and ambulatory BP [15,16]. In this regard, there are distinct ethnic differences in the impact of insulin resistance on the pathophysiological changes responsible for insulin resistance-induced increases in BP [17]. The limited impact of HOMA-IR on BP in previous studies conducted in black Africans [15] may however be explained by the use of a small study sample (n = 331) with limited power to show such relations. Moreover, in that study [15] the extent to which HOMA-IR or associated metabolic abnormalities explained obesity-associated increases in BP was not determined. Consequently, we have extended this study sample and in a markedly larger sample, using several approaches including product of coefficient mediation analysis, in the present study we aimed to determine the extent to which insulin resistance or associated metabolic abnormalities explain obesity-associated variations in office or ambulatory BP in a community of African ancestry.

2. Methods

2.1. Study group

The present study was conducted according to the principles outlined in the Helsinki declaration. The Committee for Research on Human Subjects of the University of the Witwatersrand approved the protocol (approval number: M02-04-72 and renewed as M07-04-69, M12-04-108 and M17-04-01). Participants gave informed, written consent. The present study design has previously been described [18,19]. Briefly, nuclear families (2 parents and at least 1 child or 1 parent and at least 2 children) of black African descent (Nguni and Sotho chieftoms) with siblings older than 16 years were randomly recruited from the South West Township (SOWETO) of Johannesburg, South Africa using the population census figures of 2001. In this regard, all of those families listed in this census by the South African Department of Home Affairs, living in the SOWETO region with family structures as described, were assigned a number and using a random number generator, selected for the study. As the population living in this region are predominantly from the Nguni and Sotho chieftoms, the study sample is representative for the SOWETO population. Of the 1225 participants recruited with fasting metabolic measurements, 798 participants had 24-h ambulatory BP monitoring that met with the European Society of Hypertension (ESH) guidelines (longer than 14 and 7 readings for the computation of day and night means, respectively) [20]. The prevalence of obesity, hypertension and other risk factors in the SOWETO cohort is representative of urban, developing communities of African ancestry in South Africa [21].

2.2. Clinical, demographic and anthropometric measurements

A standardized questionnaire was administered to obtain demographic and clinical data [18,19]. Height, weight, and waist (WC) and hip circumference were measured using standard approaches. Participants were identified as being overweight if their body mass index (BMI) was > 25 kg/m² and obese if their BMI was > 30 kg/m². Central (abdominal) obesity was defined as an enlarged waist circumference (> 88 cm in women and > 102 cm in men) [22]. Blood tests of renal function, liver function, fasting blood glucose, fasting lipid profile, hematological parameters, and percentage glycated hemoglobin (HbA1c) (Roche Diagnostics, Mannheim, Germany) were performed. Diabetes mellitus (DM) or abnormal blood glucose control was defined as the use of insulin or oral hypoglycemic agents or an HbA1c value greater than 6.5% [23]. Menopausal status, identified on the questionnaire, was confirmed with follicle stimulating hormone measurements. Plasma insulin concentrations were determined from an insulin immulite, solid phase, two-site chemiluminescent immunometric assay (Diagnostic Products Corporation, Los Angeles, CA, USA). Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula (insulin [µU/ml] x glucose [mmol/l])/22.5.

2.3. Office BP

High quality office BP measurements were obtained by one trained nurse according to guidelines using a standard mercury sphygmomanometer as previously described [18,19]. The nurse was of the same ethnic origins (black African) as the participants and had previously lived in SOWETO. Care was taken to use cuff-sizes commensurate with arm circumference. Hypertension was diagnosed as office systolic (SBP) > 140 mm Hg, or diastolic BP (DBP) 90 mm Hg, or the use of antihypertensive therapy [20].

2.4. Ambulatory BP

Ambulatory 24-h, day and night BP were determined using SpaceLabs monitors (model 90207) as previously described [18,19]. The size of the cuff was the same as that used for conventional BP measurements. Monitors were programmed to measure 24-h BP and pulse rate at 15-min intervals from 06:00 to 22:00 h and at 30-min intervals from 22:00 to 06:00 h. Participants kept a diary card for the duration of the recordings to note the time of going to bed in the evening and getting up in the morning. These periods were used to identify the actual in-bed and out-of-bed periods. The actual periods were used to calculate the average in-bed and out-of-bed periods for the study sample and thus the average transition periods when BP changes rapidly in most participants. These average transition periods were then eliminated. The remaining periods were considered to be the night or day fixed-clock time periods. Fixed-clock time periods rather than actual in bed and out of bed periods were statistically analyzed to ensure that similar day and night-time periods were selected for comparisons between individuals. Day and night periods ranged from 09:00 to 19:00 h and from 23:00 to 05:00 h, respectively. No participants reported on daytime ‘naps’. Intra-individual means of the ambulatory measurements were weighted by the time interval between successive readings. The average (±SD) number of BP readings obtained was 60.4 ± 12.4 (range = 24 to 81) for the 24-h period, 29.7 ± 6.5 (range = 14 to 41) for the day and 9.5 ± 0.8 (range = 7 to 11) for the night periods. Exclusion of readings obtained during the transition periods resulted in a lower number of readings for the day and night periods combined as compared to the total obtained for the 24-h period.

2.5. Data analysis

For database management and statistical analysis, SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was employed. Data are shown as mean ± SD or medians and interquartile ranges. Means, medians and proportions were compared by the large-sample z-test and the χ²-statistic, respectively. As several metabolic measurements were non-normally
distributed, to improve on the distribution, they were expressed as log (insulin, HOMA-IR and triglycerides), square root (HDL cholesterol), or the reciprocal (glucose). Multivariate relationships were determined using linear regression analysis. To determine probability values, further adjustments for non-independence of family members was performed using non-linear regression analysis (mixed procedure as defined in the SAS package). To determine the contribution of HOMA-IR and several associated metabolic parameters to BP, multivariate adjusted product of coefficient mediation analysis was performed.

To account for the effect of therapy on BP continuous relationships with BP were determined using two approaches. First, relations were determined in all participants with pretreatment brachial BP determined by using the approach described by Tobin et al., 2005 [24] of adding a sensible constant to the observed BP [24]. Pretreatment SBP and DBP values in hypertensives receiving monotherapy (11.8% of the sample) were predicted by adding weighted average class and dose-specific drug effects on BP in groups of African ancestry as previously described [25]. To impute pretreatment brachial artery BP values in hypertensives receiving dual therapy (7.8% of the sample), the average weighted percentage effect of a second drug in diuretic- or non-diuretic-treated groups of African ancestry [25] was also added to pretreatment values. In the 3.6% and 0.7% of participants receiving triple or quadruple drug therapy respectively, the average weighted percentage effect of a third or fourth drug was assumed to be similar to the average weighted percentage effect of a second drug in diuretic- or non-diuretic-treated groups of African ancestry [25] and these values were also added to pretreatment values. To predict pretreatment 24-h, day or night BP in treated participants, weighted average class and dose-specific drug effects on BP in groups of African ancestry were adjusted for differential effects of therapy on ambulatory as compared to office BP [26]. No participants were receiving more than 4 drugs.

3. Results

3.1. Participant characteristics

Participant characteristics are shown in Table S1. More women than men participated in the study. 23.3% of the study sample were overweight and 43.1% were obese, with more women than men being overweight and obese. 47.4% of the study sample had central obesity, again with more women than men having central obesity. 45.6% of participants were hypertensive. The majority of all participants had never received antihypertensive therapy (untreated).

3.2. Relationships between adiposity indexes and metabolic parameters

Independent of age, WC was associated with log insulin (partial r = 0.22, p < 0.0001), log triglyceride (partial r = 0.18, p < 0.0001), 1/ glucose (partial r = −0.15, p < 0.0001) and square root HDL cholesterol (partial r = −0.20, p < 0.0001) concentrations as well as log HOMA-IR (partial r = 0.23, p < 0.0001). Relations were similarly noted between BMI and metabolic parameters, but these relations were generally weaker (data not shown). In addition, HOMA-IR was markedly increased in participants with diabetes mellitus or an HbA1c >6.5% (Median and interquartile ranges 3.74 [1.88 to 7.08] versus 1.49 [0.76 to 2.86], p < 0.0001) and with adjustments for age, HOMA-IR was strongly correlated with log triglyceride (partial r = 0.21, p < 0.0001) and square root HDL cholesterol (partial r = −0.24, p < 0.0001) concentrations.

3.3. Multivariate-adjusted relations with BP

In separate models, independent of potential confounders, both WC and HOMA-IR (Table 1) were independently associated with office, 24-h, day or night BP. Importantly, as compared to HOMA-IR, WC produced a greater impact (standardized β-coefficient) on BP (Table 1) and no relations were noted between HOMA-IR and ambulatory DBP whilst WC was independently associated with ambulatory DBP (Table 1). With WC and HOMA-IR in the same multivariate regression models, WC retained strong and independent relations with ambulatory BP, whilst HOMA-IR failed to show independent relations with ambulatory BP and demonstrated only modest independent relations with office BP (Table 2). Independent of the individual terms, no interactions between WC and HOMA-IR were associated with office or ambulatory BP (p = 0.31 to 0.96). Importantly, the independent relations between WC and office or ambulatory BP were thus retained across tertiles of HOMA-IR (Figure S1).

Although fasting insulin and glucose concentrations were independently associated with BP (Table S2), these relations were no better than

![Table 1](image-url)

| Waist circumference or log HOMA-IR vs | Waist circumference vs BP | Log HOMA-IR vs BP |
|-------------------------------------|--------------------------|------------------|
| Partial r (95% CI) β-coef, ±SEM p-value | Partial r (95% CI) β-coef, ±SEM p-value |
| All |  |  |
| Office SBP (n = 1225) | 0.12 (0.06-0.17) | 0.114 ± 0.027 | <0.0001 | 0.09 (0.03-0.15) | 0.075 ± 0.024 | <0.005 |
| Office DBP (n = 1225) | 0.16 (0.11-0.21) | 0.175 ± 0.031 | <0.0001 | 0.08 (0.03-0.14) | 0.078 ± 0.027* | <0.005 |
| 24-h SBP (n = 798) | 0.18 (0.11-0.24) | 0.186 ± 0.037 | <0.0001 | 0.08 (0.01-0.15) | 0.067 ± 0.031* | <0.05 |
| 24-h DBP (n = 798) | 0.12 (0.05-0.19) | 0.136 ± 0.039 | <0.0005 | 0.02 (0.05 to 0.09) | 0.022 ± 0.033* | <0.51 |
| Day SBP (n = 798) | 0.17 (0.10-0.24) | 0.180 ± 0.037 | <0.0001 | 0.09 (0.02-0.16) | 0.078 ± 0.031* | <0.02 |
| Day DBP (n = 798) | 0.13 (0.06-0.19) | 0.139 ± 0.039 | <0.0005 | 0.05 (0.02 to 0.12) | 0.043 ± 0.033 | <0.19 |
| Night SBP (n = 798) | 0.17 (0.10-0.24) | 0.179 ± 0.036 | <0.0001 | 0.05 (0.02 to 0.12) | 0.041 ± 0.031** | <0.18 |
| Night DBP (n = 798) | 0.12 (0.05-0.19) | 0.133 ± 0.037 | <0.0005 | 0.02 (0.05 to 0.09) | 0.020 ± 0.032* | <0.54 |
| Untreated |  |  |  |  |  |  |
| Office SBP (n = 932) | 0.13 (0.07-0.19) | 0.132 ± 0.033 | <0.0001 | 0.08 (0.02-0.15) | 0.077 ± 0.028 | <0.01 |
| Office DBP (n = 932) | 0.18 (0.12-0.234) | 0.200 ± 0.036 | <0.0001 | 0.08 (0.01-0.14) | 0.072 ± 0.031* | <0.05 |
| 24-h SBP (n = 618) | 0.16 (0.09-0.24) | 0.180 ± 0.044 | <0.0001 | 0.09 (0.01-0.17) | 0.081 ± 0.036 | <0.05 |
| 24-h DBP (n = 618) | 0.09 (0.01-0.17) | 0.102 ± 0.045 | <0.05 | 0.03 (0.05 to 0.11) | 0.024 ± 0.036 | <0.50 |
| Day SBP (n = 618) | 0.15 (0.07-0.23) | 0.167 ± 0.044 | <0.0005 | 0.09 (0.01-0.17) | 0.080 ± 0.036 | <0.05 |
| Day DBP (n = 618) | 0.09 (0.01-0.17) | 0.107 ± 0.046 | <0.02 | 0.03 (0.05 to 0.11) | 0.027 ± 0.037 | <0.47 |
| Night SBP (n = 618) | 0.17 (0.09-0.24) | 0.183 ± 0.043 | <0.0001 | 0.06 (0.02 to 0.14) | 0.053 ± 0.036* | <0.14 |
| Night DBP (n = 618) | 0.10 (0.02-0.17) | 0.107 ± 0.044 | <0.02 | 0.03 (0.05 to 0.11) | 0.025 ± 0.036 | <0.48 |

β-coef, standardized β-coefficient with WC or HOMA-IR in separate regression models. HOMA-IR, homeostasis model of insulin resistance; SBP, systolic blood pressure; DBP, diastolic BP. “All” refers to all participants with pretreatment BP values imputed in treated participants and “untreated” refers to analysis in participants having never received antihypertensive therapy. Adjustments are for age, sex, regular tobacco use, regular alcohol consumption and the presence of diabetes mellitus. *p < 0.05, **p < 0.01 versus standardized β-coefficient for relations between waist circumference and BP.
HOMA-IR and BP (see partial r and standardized β-coefficients in table S2 versus Table 1). Moreover, fasting lipid concentrations were not independently associated with BP (Table S2).

### 3.4. Product of coefficient mediation analysis

Adjustments for HOMA-IR failed to modify the impact of a one standard deviation (SD) effect of WC on BP (Fig. 1) and in mediation analysis, HOMA-IR only accounted for a small proportion of the impact of a one SD effect of WC on either office or ambulatory BP (Fig. 1). In addition, adjustments for alternative metabolic parameters (fasting insulin, glucose, HDL cholesterol or triglyceride concentrations) failed to modify the impact of a one SD effect of WC on BP (Fig. 2) and in mediation analysis, alternative metabolic parameters accounted for none of the impact of a one SD effect of WC on either office or ambulatory BP (Fig. 2).

### 4. Discussion

The main findings of the present study are as follows: In a relatively large (n = 1225 of which 798 had ambulatory BP values) community-based sample with a high prevalence of obesity and uncontrolled hypertension we note a limited role for insulin resistance (HOMA-IR) and associated metabolic abnormalities in explaining relations between central obesity (waist circumference [WC]) and office or ambulatory BP. In this regard, although in separate regression models both WC and HOMA-IR, fasting insulin and fasting glucose concentrations (but not alternative associated metabolic parameters), were independently associated with office and ambulatory BP, when considered in the same regression model, WC retained strong relations with BP, but relations between HOMA-IR and BP were largely eliminated. Moreover, in product of coefficient mediation analysis HOMA-IR and alternative associated metabolic parameters accounted for only a negligible portion of the impact of waist circumference on office or ambulatory BP.

The role of insulin resistance and associated metabolic abnormalities as mechanisms that explain the impact of obesity on BP, is well established [5,8]. Data from large population-based cohorts of Americans or Asians suggest that up to 68% of obesity-related effects on office or clinic BP can be accounted for by insulin resistance (as indexed by HOMA-IR) or associated metabolic changes [13]. These data indicate that a primary target that could ameliorate obesity-associated effects on BP is insulin resistance and associated metabolic abnormalities. However, earlier work in a smaller sample (n = 331) of the present community suggests that groups of African ancestry show a poor relationship between HOMA-IR and BP despite significant relations between waist circumference and BP [15,16]. These data [15] were however limited by the use of a small study sample and untreated participants only, an approach that may have diminished the power to show HOMA-IR effects or resulted in the exclusion of a significant number of participants with insulin resistance. Moreover, in that study [15] we failed to identify, using mediation analysis, the relative contribution of HOMA-IR or associated metabolic abnormalities to the impact of obesity on BP. In the present study conducted in a markedly larger study sample and with the inclusion of treated participants with pre-treatment BP values imputed using standard approaches [24], we nevertheless show in mediation analysis, a limited contribution of HOMA-IR or associated metabolic abnormalities in explaining relations between waist circumference and BP despite significant relations between waist circumference and BP [15,16].

![Fig. 1. Contribution (product of coefficient mediation analysis) of the homeostasis model of insulin resistance (HOMA-IR) to the relationship between waist circumference (WC) and office or ambulatory blood pressure (BP) parameters in a community sample of African ancestry. Figures show one standard deviation (SD) effect of WC before and after adjustments (adj.) for HOMA-IR on BP and the contribution of HOMA-IR to the one SD effect of WC on BP. Adjustments are for age, sex, regular tobacco use, regular alcohol consumption, and the presence of diabetes mellitus.](image-url)
abnormalities to the relationships between obesity and BP. These data therefore suggest that insulin resistance or associated metabolic abnormalities play little role in accounting for obesity-associated increases in BP in groups of African ancestry living in Africa. Thus, despite the high prevalence of insulin resistance and type II diabetes mellitus in these populations, efforts to target insulin resistance and associated metabolic abnormalities are unlikely to produce marked effects on obesity-associated increases in BP.

Although prior studies demonstrating a strong contribution of insulin resistance to obesity-associated increases in BP in several populations with large study samples [13], the authors employed office or clinic BP alone to determine the impact of HOMA-IR. A strength of the present study is that we provide ambulatory BP data to support the results obtained with office BP measurements. In this regard, in the present study HOMA-IR showed more significant relations with office than ambulatory BP, with no independent relations noted between HOMA-IR and ambulatory DBP. In contrast, waist circumference showed independent relations with both office and ambulatory SBP and DBP. Thus, it is possible that the impact of HOMA-IR on DBP at least, is overestimated by the use of office BP. The previously reported contribution of insulin resistance to relations between adiposity indexes and office DBP [13] may therefore have overestimated the role of insulin resistance in contributing to obesity-associated increases in actual (24-h) DBP. Further studies in different population samples are therefore required to determine the contribution of insulin resistance to the impact of obesity on ambulatory DBP.

Although the use of HOMA-IR is not as accurate a method of assessing insulin resistance as alternative methods, HOMA-IR is the most convenient method of assessing insulin resistance in large community or population-based samples. Nevertheless, the use of HOMA-IR in the present study may have resulted in an underestimation of the impact of insulin resistance on BP. However, studies demonstrating a marked contribution of insulin resistance to obesity-associated increases in BP also employed HOMA-IR to assess the extent of insulin resistance [13]. Importantly, HOMA-IR in the present sample was strongly related to several metabolic parameters including lipid concentrations and the presence of diabetes mellitus. Hence, the use of HOMA-IR in the present sample is as likely to reflect the impact of insulin resistance on metabolic changes as in alternative populations.

The results of the present study support data to show a lack of impact of metformin, a well-recognised modulator of insulin sensitivity, on blood pressure, in obese hypertensives [27]. In this regard, if a reduced insulin sensitivity is of importance in mediating the BP effects of obesity, then an enhanced insulin sensitivity induced by metformin [28,29] should have beneficial effects on BP in obesity. The present and this previous [27] study together therefore suggest that in some populations, obesity effects on BP may be mediated more by factors other than insulin resistance and associated metabolic abnormalities and that targeting insulin resistance will have little consequence to BP. This does not necessarily preclude an important role for insulin resistance beyond obesity effects on BP mediated by increases in Na⁺ intake. Indeed, in-keeping with several lines of evidence we have previously demonstrated that HOMA-IR influences relations between Na⁺ intake and ambulatory BP in the present community sample [15].

In the present study we did not explore the possible reason why insulin resistance and associated metabolic abnormalities failed to explain a significant proportion of obesity-associated BP effects. In this regard however, there are distinct inter-ethnic differences in the impact of insulin resistance on sympathetic nervous system activation [17] and hence it is possible that the present study sample shows similar differences. A further limitation of the present study is that we did not evaluate the numerous alternative factors thought to play an important role in obesity-induced increases in BP [5–11]. However, in previous publications [30] significant associations between adiposity indexes and the circulating renin-angiotensin-aldosterone system were not observed in the present community sample. Nevertheless, whether obesity-associated BP changes in the present community sample can be explained by alterations in mineralocorticoid or renal effects or the impact of adipocytokines on the vasculature or the activity of the sympathetic nervous system [5,8], requires further study.

In conclusion, in the present study conducted in a group of African ancestry, we show that despite marked associations between HOMA-IR
and metabolic changes, that in contrast to alternative populations [13], HOMA-IR and associated metabolic changes account for little of the impact of central obesity on office or ambulatory BP. Targeting insulin resistance and associated metabolic changes is therefore unlikely to markedly ameliorate the impact of obesity on BP in populations of African descent.

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Conflict of interest/disclosures

None.

Author contribution

AJB, GRN and AJW take responsibility for drafting of the manuscript, critically revising the manuscript for intellectual content, conception and design of the study, analysis and interpretation of the data and final approval of the manuscript submitted.

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Appendix A. Supplementary data

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