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Dietary Intake Analyses for the Pharmacometrics to Advance Novel Regimens for Drug-resistant Tuberculosis (PandrTB) Pharmacokinetic Sub-Study of the endTB and endTB-Q Clinical Trials

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Short Report

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Abstract

Objective:

Food consumed with anti-tuberculosis drugs can significantly affect their pharmacokinetics, potentially facilitating the development of resistance and impacting efficacy and safety. We describe dietary intake data from the PandrTB study, which evaluated the pharmacokinetics of bedaquiline, clofazimine, delamanid, levofloxacin, linezolid, moxifloxacin, and pyrazinamide in persons with drug-resistant TB. Dietary intake was recorded to assess the potential influence of concomitant food on drug absorption.

Results:

From 144 PandrTB study participants, 1030 meals were analyzed. The fat content of morning meals was <30% for 37.18% of meals on the day before the pharmacokinetic visit, and 16.76% of meals on the sampling day at the study facility. The median intake of nutrients in the morning meal was higher at the study facility than on the day before the pharmacokinetic visit ($p < 0.05$), except for calcium. More than 50% of morning meals contributed ≤50% of the Estimated Average Requirements for all nutrients, except for iron, on the day of the pharmacokinetic visit. Comparison of morning and evening meals the day before the pharmacokinetic visit showed trends to higher median total energy, magnesium, and zinc contents for the evening meal, while fat, calcium, and iron content tended to be higher in the morning meal.

Introduction

Despite the slight decline in tuberculosis (TB) incidence and deaths in 2024, TB remains the world's leading infectious killer, with uneven regional progress and funding shortfalls threatening the achievement of the 2030 End TB targets [1]. Developing new drugs and treatment regimens is crucial to improving patient outcomes and to combat this public health issue [2].

Drug resistance in TB can stem from incomplete treatment and pharmacokinetic (PK) interactions, including dietary influences on drug absorption [3,4]. Co-administration of key second-line antituberculosis (anti-TB) agents, bedaquiline and clofazimine, with food greatly increases their bioavailability [2,3,5]. Certain minerals, such as calcium, iron, magnesium, zinc, and aluminium, can reduce the absorption of fluoroquinolones (moxifloxacin and levofloxacin) due to chelation-based interactions [6]. These dietary factors contribute to variability in drug concentrations, possibly impacting drug efficacy and safety, as well as potentiating the development of drug resistance, limiting the utility of new drugs [7].

Regulatory agencies such as the U.S. Department of Health and Human Services, Food and Drug Administration (FDA), and Center for Drug Evaluation and Research (CDER) require food effect studies during the drug evaluation process, and often use high-calorie, high-fat meals to evaluate the effect of food on drugs [7]. A high-fat meal is classified as providing more than 50% of the caloric intake from fat

[7]. This type of meal is chosen because it has the greatest effect on gastrointestinal physiology and the bioavailability of many oral drugs [7].

Many TB patients struggle with adequate nutrition due to poor appetite and socioeconomic factors, leading to undernutrition, which is highly prevalent amongst them and can significantly impact treatment outcomes [8–13]. Therefore, it is important to collect and record good-quality dietary data to observe any food-drug interactions.

This article describes dietary intake data of patients from multiple countries who participated in the Pharmacometrics to Advance Novel Regimens for Drug-Resistant Tuberculosis (PandrTB, NCT03827811), PK sub-study of the endTB (NCT02754765), and endTB-Q (NCT03896685) clinical trials. Drugs evaluated in the PandrTB sub-study included bedaquiline, clofazimine, delamanid, levofloxacin, linezolid, moxifloxacin, and pyrazinamide, some of which are subject to notable food-effects [14–20]. The multinational scope of the PandrTB sub-study enhances the generalizability of its findings across diverse populations and dietary contexts, strengthening its relevance for global TB treatment strategies. Dietary intake was recorded as it was expected that the intake of concomitant food, particularly fat, might affect the absorption of the drugs.

Methods

PandrTB is an observational, multi-country PK sub-study involving participants from the experimental arms of the endTB and endTB-Q (Phase III randomized, controlled clinical trials testing shorter regimens for rifampicin-resistant TB and sponsored by Médecins Sans Frontières). The study included participants of the endTB and endTB-Q trials who provided separate written informed consent to participate in the PK sub-study, aged 15 years or older, and were recruited from Kazakhstan, Lesotho, Pakistan, Peru, South Africa, and Vietnam.

Recorded dietary data included food consumed within two hours before and/or after taking TB treatment on the day before and on the PK sampling day (see **Table S1** – an excerpt of the dietary data collection form). Food intake before the PK visit, taken at the participant's home, was assumed to reflect the participant's usual dietary habits. On the PK sampling day, the study provided morning meals at the study site

The variables extracted from the database included dietary data captured at the three PK visits during TB treatment, country, and date of food consumption. Fieldworkers were contacted via email to describe country-specific food items (regarding probable quantities consumed and food preparation methods), and a dietary coding team was engaged to analyze the data. The South African Medical Research Council (SAMRC) Food Quantities Manual (FQM) was utilized to determine the average quantities of food consumed [21]. If food quantities and types of food, as well as cooking methods, were not mentioned, assumptions were made (see **Table S2**) [22]. Once the dietary data were coded, the energy, fat, and mineral content for each meal was calculated in Microsoft Excel using the SAMRC Food Composition Tables (FCT) [23]. Calcium, iron, magnesium, and zinc were included due to their potential

interaction with anti-TB drugs [24]. Total energy for each meal was calculated before classification according to the fat content, where ≥50% of energy from fat would indicate a high-fat meal [7]. Additional fat content categories (<30%, 30% to <40%, and 40% to <50% of energy) were calculated to facilitate sensitivity analysis. The analyses were done using IBM SPSS Statistics version 30. The Wilcoxon Signed-Rank Test was applied to compare dietary intake differences between the morning meals of the two days, as well as the morning and evening meal for the day before PK sampling.

Results

PandrTB enrolled 144 participants from six countries, with 92 (63.89%), 23 (15.97%), and 29 (20.14%) participants undergoing PK sampling on 3, 2, and 1 occasion, respectively (see **Figure 1** - a breakdown of the PK visits and meals analyzed for both days). In total, 1030 meals were analyzed.

The fat content of morning meals was <30% for 37.18% and 16.76% of meals, respectively, on the day before and on the PK day (**Table 1**). Few meals were classified as having a fat content of >50 % of the total energy, with the majority of these meals being consumed on the PK day (before the PK visit, 69 meals vs 78 meals on the PK day). Except for calcium, we found nutrient intake was lower on the day before PK (**Table 1**) (**Figure 2** shows the distribution of the nutrients in boxplots).

Nutrient contribution was determined for both days by comparing the intake to the Estimated Average Requirements (EAR) (see **Table S3**). The EAR was used to interpret the data, as it represents the daily intake level estimated to meet the requirements of 50% of healthy individuals within a specific population or group, whereas the Recommended Daily Allowance (RDA) is designed for individuals [25]. This approach is suitable for population-level assessment (adults aged 19–50 years), especially when detailed demographic data are unavailable (see **Table S4**) [25]. We selected the highest EAR values for the age range 19 – 50 years to prevent underestimation [25]. **Figure 3** shows that most morning meals for both days contributed to ≤50% of the EAR for all nutrients, with about 90% of these meals contributing ≤25% of the EAR for calcium. On the PK visit day, 40% of the meals contributed 50 to 75% of the iron EAR. For magnesium, about 70% of the morning meals for both days contribute ≤25% of the EAR. On both days majority of the meals contributed between 25% and 50% of the EAR for zinc.

A comparison of 105 paired morning and evening meals (see **Table 2**) was done for the day before the PK visit, and no significant differences were found ($p>0.05$). The combined intake from the two meals for more than 70% of the participants contributed to ≤50% of the EAR for calcium and magnesium (see **Figure 4**). However, for iron and zinc, the total intake contributed to ≥50% of the EAR for the majority of the participants. Also, for iron and zinc, >25% of participants' intake from the morning and evening meal exceeded 100% of the EAR.

Discussion and Conclusion

The fat content in the meals showed that only a small percentage were high-fat, the majority of which were provided by the study team during PK sampling, and based on readily available foods at the facility.

Additionally, we found that most morning meals for both days contributed to ≤50% of the EAR for all the nutrients, contrasting with the high-fat meals typically provided to assess the effect of food on PK during drug development [7]. The differences observed ($p < 0.05$) (see **Table 1**) in morning meals for the two days may result from individual dietary preferences, food choices, food accessibility, affordability, and the standardized nature of the meals provided by the study team. Also, it is possible that factors not captured in the dietary assessment (e.g., cooking methods) could have influenced meal composition. Although our findings showed that the facility-provided morning meal contributed more to the EAR for most nutrients than the at-home morning meal, only one meal was analyzed. Therefore, total daily adequacy cannot be assumed. Furthermore, we found that a higher proportion of participants contributed ≥50% to the calculated EAR on the day before the PK visit for iron and zinc (see **Figure 4**).

The energy and nutrient distribution often depend on culture and eating patterns [26–28]. The evening meal showed a trend to higher nutrient content compared to the morning meal. This tracks with what is shown in literature, which is that in many populations, the evening meal usually provides the greatest energy and fat contribution, and also a significant portion of nutrient intake [26–28]. However, our comparison between the morning and evening meals on the day before the PK day did not find significant differences in nutrient content, and therefore cannot inform whether drugs should be taken with the morning or evening meal.

The observed variability in energy, fat, and cation content confirms the importance of recording the meal content of participants in PK studies. This variability highlights the need to understand how daily dietary intake influences the PK of anti-TB drugs. To achieve this, detailed descriptions of the eating time, type of food, ingredients, cooking methods, and amounts are critical to allow accurate meal content analyses and reduce analytical bias [29]. Moreover, implementing standardized procedures, the inclusion of dietary intake specialists in the design of the study, and existing or specially developed manuals on dietary intake may be beneficial [30]. Extending the period of dietary intake recall to allow for an understanding of the usual daily intake of participants may also be useful. By addressing these methodological considerations, future PK studies can improve the reliability of dietary data and provide better insights into food-drug interactions, ultimately enhancing participant compliance and the interpretability of PK outcomes.

Limitations and Recommendations

· Data was collected only two hours before or after TB treatment, thus limiting insights into participants' daily intake. The lack of detail about food quantity, type, and preparation hinders the process of accurately assessing the relative and absolute fat content. As a result, many assumptions were made about the food quantity and cooking methods. Due to self-reporting and recall data not being detailed, we can assume that information bias exists.

o To improve dietary data collection, it is important to consult with diet and nutrition specialists to provide comprehensive training for fieldworkers on dietary assessment methods, as this will enhance their ability to accurately describe dietary intake [31]. Also, implementing detailed dietary recalls, encouraging food diaries, and expanding data collection to include all daily meals will help address limitations and reduce bias [31]. The use of more than one dietary recall method can help to accurately assess daily dietary intake [32].

· South African resources (the SAMRC-FQM and the SAMRC-FCT) were used across diverse settings. This likely led to some inaccuracy and masks variability in nutritional content deriving from differences in food items, growing conditions, and processing methods [33]. This can lead to discrepancies between the actual nutrient content in consumed foods and the values listed in the SAMRC-FCT. Additionally, the tables may not always reflect the latest data, which can further limit their accuracy [23,34]. This can therefore skew the assessment of nutrient intake, especially zinc, which is particularly at risk of the above challenges.

o While using FCT from one country for standardization purposes, it is also important to incorporate country-specific food composition databases that reflect indigenous meals and preparation methods [35].

· Finally, due to missing demographic data, we used the highest EAR values for the 19-50 age group to avoid underestimating dietary intake.[25].

o It is important to include all demographic and socioeconomic information to accurately interpret dietary data.

Abbreviations

PandrTB: Pharmacometrics to Advance Novel Regimens for Drug-resistant Tuberculosis

PK: Pharmacokinetics

end-TB: Expand new drug markets for tuberculosis

endTB-Q: Evaluating Newly approved Drugs in combination regimens for multidrug-resistant Tuberculosis with fluoroquinolone resistance

SAMRC: South African Medical Research Council

FQM: Food Quantities Manual

FCT: Food Composition Tables

EAR: Estimated Average Requirements

RDA: Recommended Daily Allowances

Declarations

Ethics approval and consent to participate

This study involves a secondary analysis of anonymous dietary data collected as part of the approved clinical trial NCT03827811 [Pharmacometrics to Advance Novel Regimens for Drug-resistant Tuberculosis (PandrTB)]. No additional participant contact happened, and no identifiable information was accessed. The secondary analysis was conducted in accordance with the relevant institutional guidelines for the secondary use of research data.

The PandrTB sub-study, registered on ClinicalTrials.gov on 07/08/2018, received ethical approval from all relevant institutional research ethics committees, including the University of Cape Town, Faculty of Health Sciences Human Research Ethics Committee (HREC), the local institutional review boards for sites contributing data, and the ethics committees of Médecins Sans Frontières and Harvard Medical School. Written informed consent was obtained from all participants before enrolment. The trial was conducted in compliance with the ethical principles of the Declaration of Helsinki (2013), the principles of the International Conference for Harmonization Good Clinical Practice (ICH-GCP) guidelines, and applicable national regulations.

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusions of this article (and its additional file) is available in the **Kikapu** repository (UWC's Institutional Data Repository powered by Figshare for Institutions).

Competing interests

Loren Hans (LH) receives funding for postgraduate studies (Masters) from the National Research Foundation (NRF)*.

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Authors' contributions

LH created the primary manuscript for the review and performed the dietary coding and analysis of the dietary data.

RS oversaw the dietary coding process and participated in the review of various drafts of the research note.

HM designed and oversaw the collection of the data and participated in the review of various drafts of the research note.

Gustavo E. Velásquez, Carole D. Mitnick, Lorenzo Guglielmetti, Francis Varaine: all contributed to oversight and overall responsibility for conduct of the endTB and endTB-Q clinical trials

Fanny Garcia Velarde, Mahnoor Sahiba Arshad, Azhar Magzumova, Assel Stambekova, Sesomo Mohale, Hanh T.T. Nguyen:All responsible for execution of the study and data collection

*All authors reviewed and approved of the final version of this paper

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Tables

Table 1: Dietary intake of participants (PandrTB Sub-Study) for the morning meal before and on the PK day.

Morning meal	before PK visit (at home)	on the PK day (at clinic)	p-value
	n = 347	n = 352	
Energy (TE) content per meal (kJ)			
Median (min – max)	1969.15 (0.00 – 6231.96)	2290.95 (0.00 – 5190.90)	0.019
Fat content per meal (kJ)			
Median (min – max)	623.91 (0.00 – 3774.45)	869.83 (0.00 – 3041.81)	<0.001
Fat classification (per meal): n (%)			
< 30%	129 (37.18)	59 (16.76)	
≥ 30 to < 40 %	59 (17.00)	111 (31.53)	
≥ 40 to < 50 %	90 (25.94)	104 (29.55)	
≥ 50	69 (19.88)	78 (22.16)	
CATIONS per meal			
Calcium (Ca) (mg)			
Median (min – max)	62.32 (0.00 – 425.38)	56.25 (0.00 – 509.54)	0.733
Iron (Fe) (mg)			
Median (min – max)	3.27 (0.00 – 16.48)	4.24 (0.00 – 13.70)	<0.001
Magnesium (Mg) (mg)			
Median (min – max)	62.68 (0.00 – 168.15)	72.25 (0.00 – 191.44)	0.010
Zinc (Zn) (mg)			
Median (min – max)	3.25 (0.00 – 16.39)	4.49 (0.00 – 9.90)	<0.001

*Significant difference between variables (before PK visit and on the PK day) at a p-value <0.05.

Table 2: Comparison of the dietary intake for paired meals on the day before the PK study.

	Morning meal	Evening meal	p-value
	n = 105	n = 105	
Energy (TE) content per meal (kJ)			
Median (min – max)	1978.83 (747.33 – 6231.96)	2109.81 (485.13 – 8382.25)	0.429
Fat content per meal (kJ)			
Median (min – max)	628.29 (41.04 – 3774.45)	545.87 (17.10 – 5297.73)	0.226
CATIONS per meal			
Calcium (Ca) (mg)			
Median (min – max)	61.22 (6.29 – 425.38)	58.38 (3.00 – 908.50)	0.401
Iron (Fe) (mg)			
Median (min – max)	3.28 (0.80 – 16.48)	3.24 (0.59 – 14.75)	0.787
Magnesium (Mg) (mg)			
Median (min – max)	63.65 (17.00 – 152.00)	66.18 (14.18 - 249.00)	0.519
Zinc (Zn) (mg)			
Median (min – max)	3.27 (0.40 – 16.39)	3.38 (0.35 – 15.17)	0.889

*Significant difference between variables at a p-value <0.05.

Figures

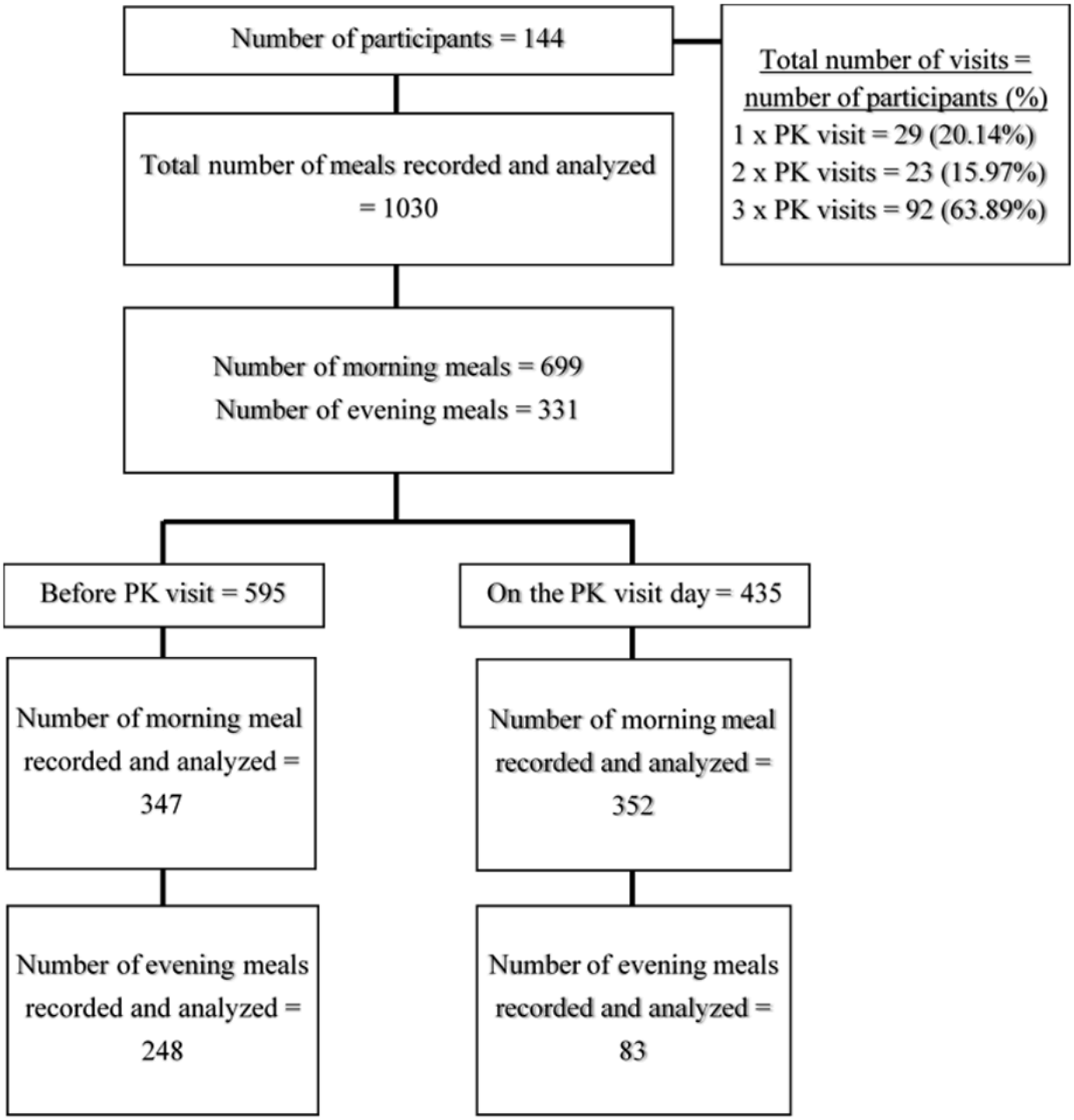


Figure 1

PK visits and meals that were recorded and analysed before and on the PK visit day.

This figure shows a visual breakdown of the number of PK visits attended by participants (n = 144) and the meals analysed (n =1030) for the day before and on the PK visit day. (Meals were included in the analyses only if data were available. Meals that were not recorded/blank/unknown were excluded from analyses.)

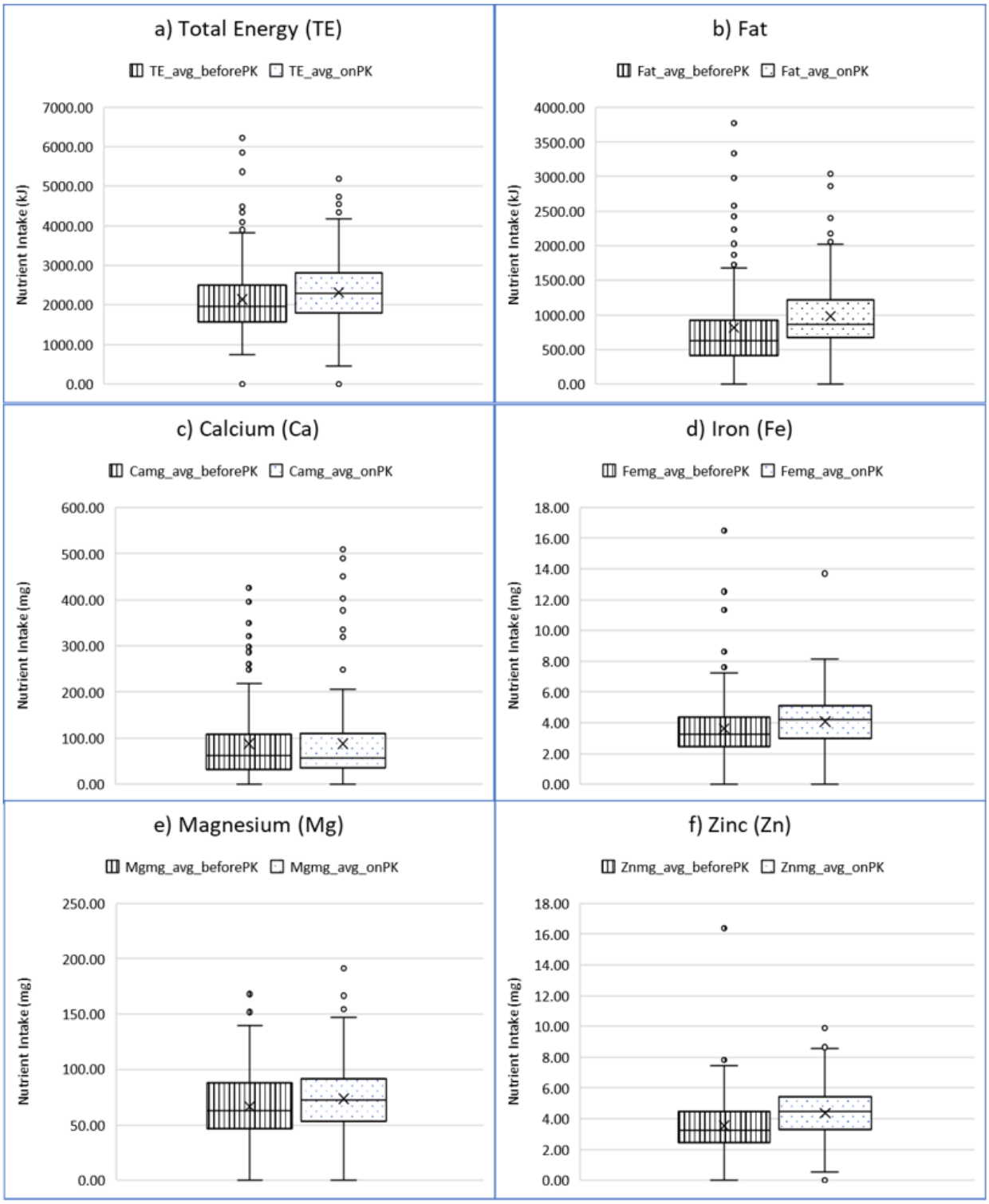


Figure 2

a - f: Distribution of the nutrient intake for MEAL 1 before and on the day of PK sampling

This figure shows the distribution of the nutrients (total energy, fat, calcium, iron, magnesium, zinc) in boxplots, where the striped box represents the nutrient intake for the day before the PK visit, and the dotted box represents the nutrient intake for the day of the PK visit.

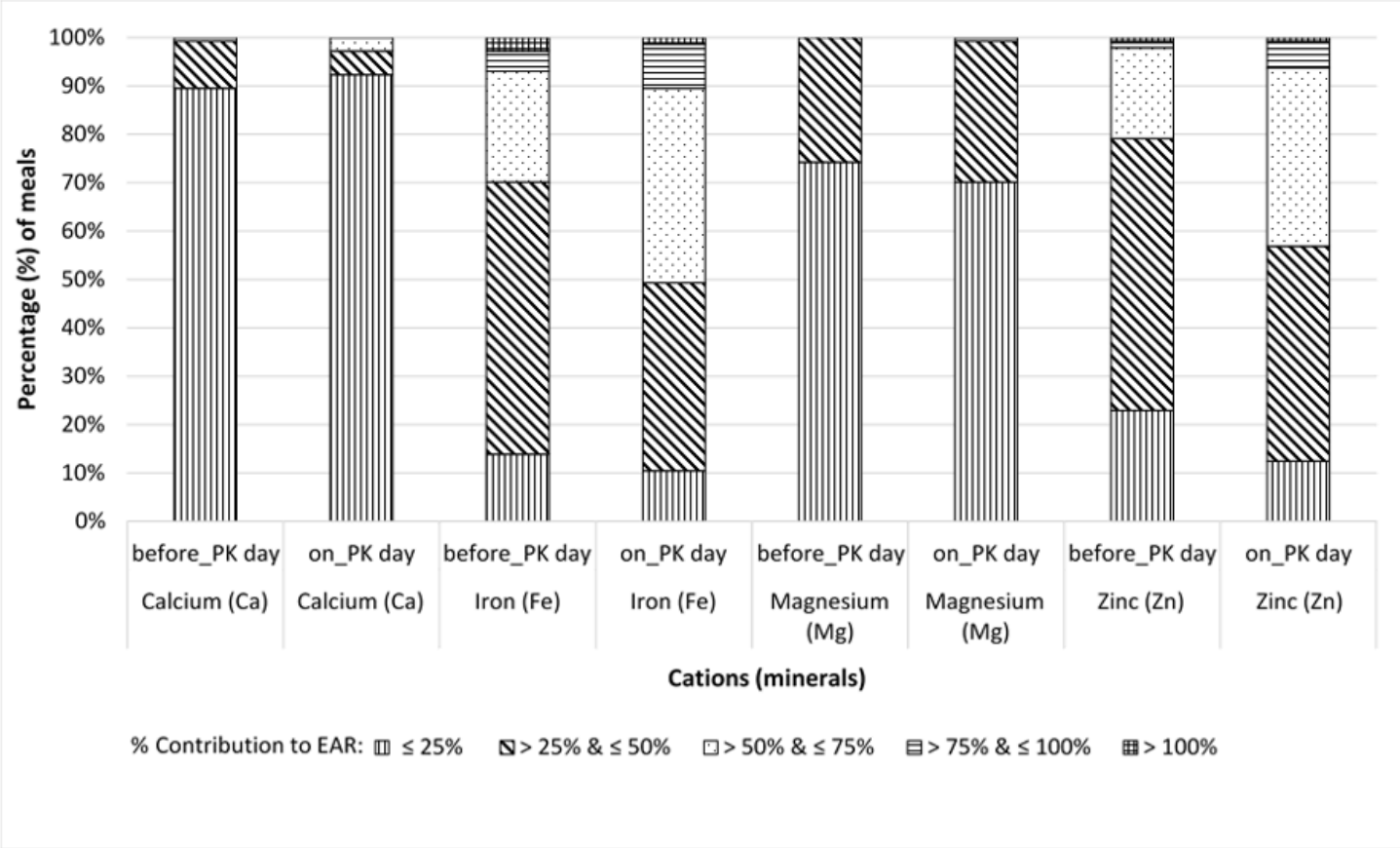


Figure 3

Morning meal contribution (day before and on the PK day) to the EAR for each nutrient

This figure shows the morning meal contribution, for the day before and the of the PK visit, to the calculated EAR (see **Table S4**) of each nutrient (calcium, iron, magnesium, zinc).

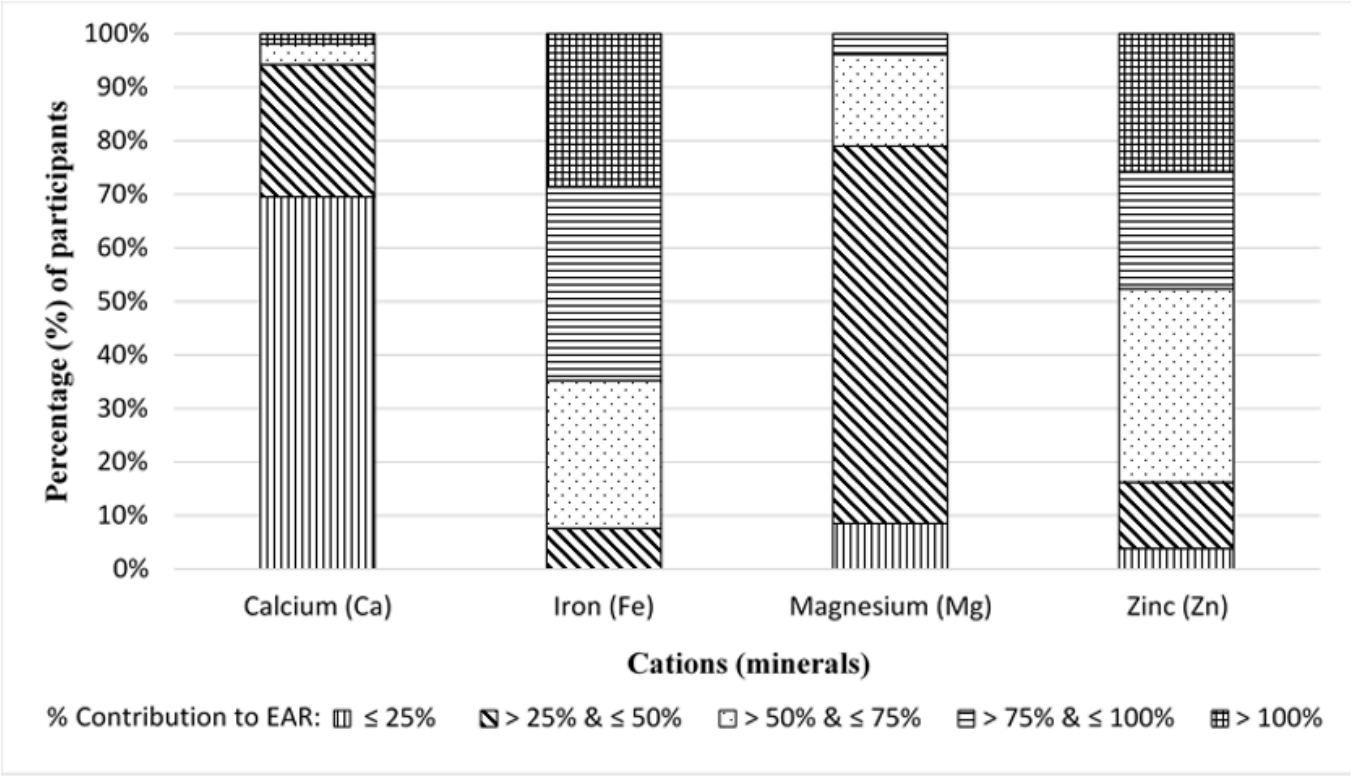


Figure 4

Contribution of total nutrient intake for the day before the PK visit, to the EAR for each nutrient

This figure shows the combined intake from the two meals, for the day before the PK visit, to the calculated EAR (see **Table S4**) of each nutrient (calcium, iron, magnesium, zinc).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile1.docx
- SupplementaryTables.docx