Risk of death following chikungunya virus disease in the 100 Million Brazilian Cohort, 2015–18: a matched cohort study and self-controlled case series

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Summary

Background Chikungunya virus outbreaks have been associated with excess deaths at the ecological level. Previous studies have assessed the risk factors for severe versus mild chikungunya virus disease. However, the risk of death following chikungunya virus disease compared with the risk of death in individuals without the disease remains unexplored. We aimed to investigate the risk of death in the 2 years following chikungunya virus disease.

Methods We used a population-based cohort study and a self-controlled case series to estimate mortality risks associated with chikungunya virus disease between Jan 1, 2015, and Dec 31, 2018, in Brazil. The dataset was created by linking national databases for social programmes, notifiable diseases, and mortality. For the matched cohort design, individuals with chikungunya virus disease recorded between Jan 1, 2015, and Dec 31, 2018, were considered as exposed and those who were arbovirus disease-free and alive during the study period were considered as unexposed. For the self-controlled case series, we included all deaths from individuals with a chikungunya virus disease record, and each individual acted as their own control according to different study periods relative to the date of disease. The primary outcome was all-cause natural mortality up to 728 days after onset of chikungunya virus disease symptoms, and secondary outcomes were cause-specific deaths, including ischaemic heart diseases, diabetes, and cerebrovascular diseases.

Findings In the matched cohort study, we included 143 787 individuals with chikungunya virus disease who were matched, at the day of symptom onset, to unexposed individuals using sociodemographic factors. The incidence rate ratio (IRR) of death within 7 days of chikungunya symptom onset was 8·40 (95% CI 4·83–20·09) as compared with the unexposed group and decreased to 2·26 (1·50–3·77) at 57–84 days and 1·05 (0·82–1·35) at 85–168 days, with IRR close to 1 and wide CI in the subsequent periods. For the secondary outcomes, the IRR of deaths within 28 days after disease onset were: 1·80 (0·58–7·00) for cerebrovascular diseases, 3·75 (1·33–17·00) for diabetes, and 3·67 (1·25–14·00) for ischaemic heart disease, and there was no evidence of increased risk in the subsequent periods. For the self-controlled case series study, 1933 individuals died after having had chikungunya virus disease and were included in the analysis. The IRR of all-cause natural death within 7 days of symptom onset of chikungunya virus disease was 8·75 (7·18–10·66) and decreased to 1·59 (1·26–2·00) at 57–84 days and 1·09 (0·92–1·29) at 85–168 days. For the secondary outcomes, the IRRs of deaths within 28 days after disease onset were: 2·73 (1·50–4·96) for cerebrovascular diseases, 8·43 (5·00–14·21) for diabetes, and 2·38 (1·33–4·26) for ischaemic heart disease, and there was no evidence of increased risk at 85–168 days.

Interpretation Chikungunya virus disease is associated with an increased risk of death for up to 84 days after symptom onset, including deaths from cerebrovascular diseases, ischaemic heart diseases, and diabetes. This study highlights the need for equitable access to approved vaccines and effective anti-chikungunya virus therapeutics and reinforces the importance of robust vector-control efforts to reduce viral transmission.

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Introduction

The global burden of arthropod-borne virus (arbovirus) diseases has substantially increased in recent years, with chikungunya virus now affecting over 110 countries worldwide.[1]

In Brazil, chikungunya virus has spread nationwide since its introduction in 2013, with all states reporting autochthonous cases. From January to June, 2023, approximately 200 000 new cases of chikungunya virus infection were registered in Brazil.[2] Although chikungunya virus disease shares similar acute symptoms with other arbovirus diseases,[3] it can cause long-lasting arthralgia in about half of symptomatic patients, substantially impacting quality of life and

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For the Portuguese translation of the abstract see Online for appendix 1

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Research in context

Evidence before this study

We searched PubMed from database inception to Aug 30, 2023, with no language restrictions, for relevant published articles using the search terms "chikungunya" AND "complication" OR "sequelae" OR "burden" OR "mortality" OR "death" OR "fatal". We found 43 articles evaluating the economic burden or long-term sequelae of chikungunya virus disease. In one study, the estimated cost per patient of chikungunya virus disease was up to US$767 when accounting for direct costs and loss of productivity. In 21 studies, the most frequent sequela was chronic arthralgia, which can last for more than 2 years after disease onset, substantially impacting the quality of life of affected individuals. We also identified seven ecological studies investigating excess mortality after chikungunya virus disease outbreaks. All studies were conducted in low-income and middle-income countries and reported between 600 and 4900 excess deaths after the outbreaks. We found three systematic reviews, one of which included a meta-analysis evaluating the risk factors for severe chikungunya virus disease. The primary risk factors associated with severe cases included the presence of underlying chronic conditions, mainly diabetes. All three reviews included only cases of chikungunya virus disease, comparing severe cases with mild ones. We could not find any study comparing the risk of death between individuals who were exposed and those unexposed to chikungunya virus disease.

Added value of this study

To our knowledge, this is the first study to triangulate evidence at the individual level on the risk of death after chikungunya virus disease using a matched cohort and a self-controlled case series. Using data from the 100 Million Brazilian Cohort, we observed a prolonged risk of death that was approximately eight times higher in people who had chikungunya virus disease (incidence rate ratio 8·40, 95% CI 4·83–20·09) than in unexposed individuals in the first week, decreasing to two times higher up to 12 weeks (2·26, 1·50–3·77). The increased risk was present independent of age group and sex, and specific causes of death included cerebrovascular diseases, ischaemic heart diseases, diabetes, and kidney diseases within 84 days of symptom onset. Individuals aged 60 years or younger experienced lower absolute risks of death following chikungunya virus disease than older individuals. However, as compared with unexposed individuals within the same age groups, individuals in the younger age group had higher relative risks of death following chikungunya virus disease than their older counterparts. Regarding sex, males presented higher absolute and relative risks of death following chikungunya virus disease.

Implications of all the available evidence

Our findings suggest that new guidelines for managing chikungunya virus disease should highlight the increased risk of death that persists after the acute phase of the disease. Risk classification and clinical management should include evaluating and monitoring cerebrovascular, cardiovascular, metabolic, and renal systems. This study reinforces the importance of ensuring equitable access to vaccines in countries with recurrent outbreaks as early as they become approved and of research and development of effective therapeutic interventions against chikungunya virus. Furthermore, reinforcing measures to control the spread of mosquitoes carrying chikungunya virus is also essential for reducing the excess mortality associated with the disease.

leading to loss of productivity years.[4] Although the first vaccine for chikungunya virus has been submitted for approval in the USA, there is currently no vaccine available in endemic countries, and specific antiviral treatments and antibody-based therapeutic interventions for chikungunya virus remain in development.[5,6]

Over the past 40 years, studies have consistently shown that infectious diseases might increase the risk of developing and decompensating non-communicable diseases, potentially leading to serious outcomes such as stroke, acute myocardial infarction, and neurological disorders.[7,8] In the case of chikungunya virus, sporadic cases of atypical complications, including neurological, cardiac, and renal manifestations, have been observed.[9,10] Some ecological studies have also revealed excess mortality following chikungunya virus outbreaks, primarily affecting individuals with pre-existing medical conditions and those aged 60 years and older.[10,11] Additionally, pre-existing diabetes has been associated with severe chikungunya virus disease.[12] Nevertheless, the evidence regarding the increased risk of severe outcomes after chikungunya virus disease primarily derives from relatively small studies and ecological approaches.[11,13,14]

Leveraging nationwide administrative data from the 100 Million Brazilian Cohort, this study aims to investigate the relative risk of death in the 2 years following chikungunya virus disease. Specifically, we aim to (1) compare the risk of death between chikungunya virus-exposed and unexposed individuals over time and by cause of death and (2) assess whether there is a difference in the risk of death following chikungunya virus disease by sex and age.

Methods

Study design and databases

We triangulated evidence between a matched cohort and a self-controlled case series to examine the risk of death following chikungunya virus disease, using approaches that rely on different key sources of potential bias and, additionally, an outcome-negative control study to evaluate the level of residual confounding in our analyses.

We used data from the 100 Million Brazilian Cohort[15] linked with nationwide death and chikungunya virus registries. The 100 Million Brazilian Cohort is a retrospective dynamic cohort that includes over 130 million individuals from the Unified Registry for Social Programs (CadÚnico). We linked the CadÚnico database to chikungunya, dengue, and Zika virus disease records from Jan 1, 2007, to Dec 31, 2018, registered in the National Notifiable Disease Information System (SINAN) and the Mortality Information System (SIM). The Research Ethics Service Committee of Instituto Gonçalo Moniz – FIOCRUZ approved the study (CAAE: 44283621.6.0000.0040). Databases and linkage accuracy are detailed in appendix 2 (pp 4–6).

Exposure and outcomes

The main exposure was an individual's first SINAN record of symptomatic chikungunya virus disease confirmed by clinical-epidemiological criteria (presence of clinical symptoms of chikungunya in the same area and time as other confirmed cases of chikungunya) or laboratory criteria (serology or nucleic acid amplification test). Individuals with chikungunya virus disease recorded between Jan 1, 2015, and Dec 31, 2018, were considered as exposed (or cases); individuals who were arbovirus virus (chikungunya virus, dengue virus, and Zika virus) disease-free and alive during the study period were considered as unexposed (or controls).

The primary outcome was all-cause natural mortality (all codes excluding external causes of death [Chapter XX] from International Classification of Diseases [ICD]-10). Secondary outcomes were cause-specific deaths defined by ICD-10 code, specifically: cerebrovascular diseases (ICD-10 I60-I69),[9] diabetes (ICD-10 E10-E14),[12] and ischaemic heart diseases (ICD-10 I20-I25).[16] Kidney diseases (ICD-10 N10-N19)[17] were evaluated in a post-hoc analysis.

The deaths due to external causes (Chapter XX of ICD-10), which are not causally associated with chikungunya virus disease, were used as an outcome-negative control.[18] We considered only the ICD-10 code recorded as the primary cause of death for all analyses.

Matched cohort design: study population and statistical analysis

Exposed individuals were exactly matched without replacement to an unexposed individual on the day of symptom onset of chikungunya virus disease according to a set of potential confounders selected a priori (appendix 2 p 21): age in years at disease onset, sex, race or ethnicity, municipality of residence, household location, household's water supply type, and education level (appendix 2 pp 4–7). Controls matched on a given day who acquired chikungunya virus disease on a subsequent date became a case and could be matched to a new control. For this analysis, we excluded (1) individuals with records of chikungunya virus, dengue virus, or Zika virus diseases before the date of entry in the 100 Million Brazilian cohort; (2) records of chikungunya virus disease outside the study period; (3) records of multiple arbovirus infections on the same date; (4) records of dengue virus or Zika virus disease before chikungunya virus disease; (5) records of dengue virus, Zika virus, or chikungunya virus infections with inconclusive results; (6) individuals with date chronology inconsistency (eg, death date earlier than entry cohort date); and (7) individuals with missing data in any matching variables. Appendix 2 (pp 5–7) shows details on matching and exclusion criteria.

Each matched pair was followed up from the matching date (date of symptom onset of the chikungunya virus disease case) until the earliest of the following events: chikungunya virus, dengue virus, or Zika virus disease, death, 728 days (104 weeks) of follow-up, or Dec 31, 2018 (final date of data collection). Censoring due to dengue virus or Zika virus disease was implemented to mitigate the potential for chikungunya virus's effects to be magnified by a co-infection. The start of the timescale of the study was time since symptom onset or the time since matching for controls.

See Online for appendix 2

We estimated the cumulative incidence of each outcome using the Kaplan-Meier estimator. We estimated period-specific incidence rate ratios (IRRs), risk differences, and risk ratios (RRs), comparing the exposed group against the unexposed group for each outcome. The period-specific intervals were demarcated on days 7, 14, 28, 56, 84, 168, 364, and 728. Individuals with the same date of death and symptom onset were excluded from the analysis. For the secondary outcomes, the period-specific intervals were stratified on days 28, 56, 84, 168, 364, and 728 due to the reduced sample size for specific causes of death. We used Cox models to estimate hazard ratios (HRs) over the first 84 days separately in the following subgroups: sex (female, male) and age groups (<60, ≥60 years).[3] We estimated the effect modification on additive and multiplicative scales by subgroups. The additive scale is a comparison of the joint effect versus the sum of individual effects in the absolute risk, whereas the multiplicative scale quantifies the combined effect versus the product of the individual effects in the relative effects across strata. We used a non-parametric bootstrapping procedure (resampling only matched pairs) with 500 iterations to calculate percentile-based 95% CIs for IRRs, risk differences, RRs, and HRs.

Sensitivity analyses were performed restricting the chikungunya virus-exposed group to individuals with laboratory-confirmed disease to evaluate the effect due to exposure misclassification and changing the matching criteria.

Self-controlled case series study population and statistical analysis

The self-controlled case series design uses only cases, and each individual acts as their own control, eliminating confounding due to time-invariant characteristics.

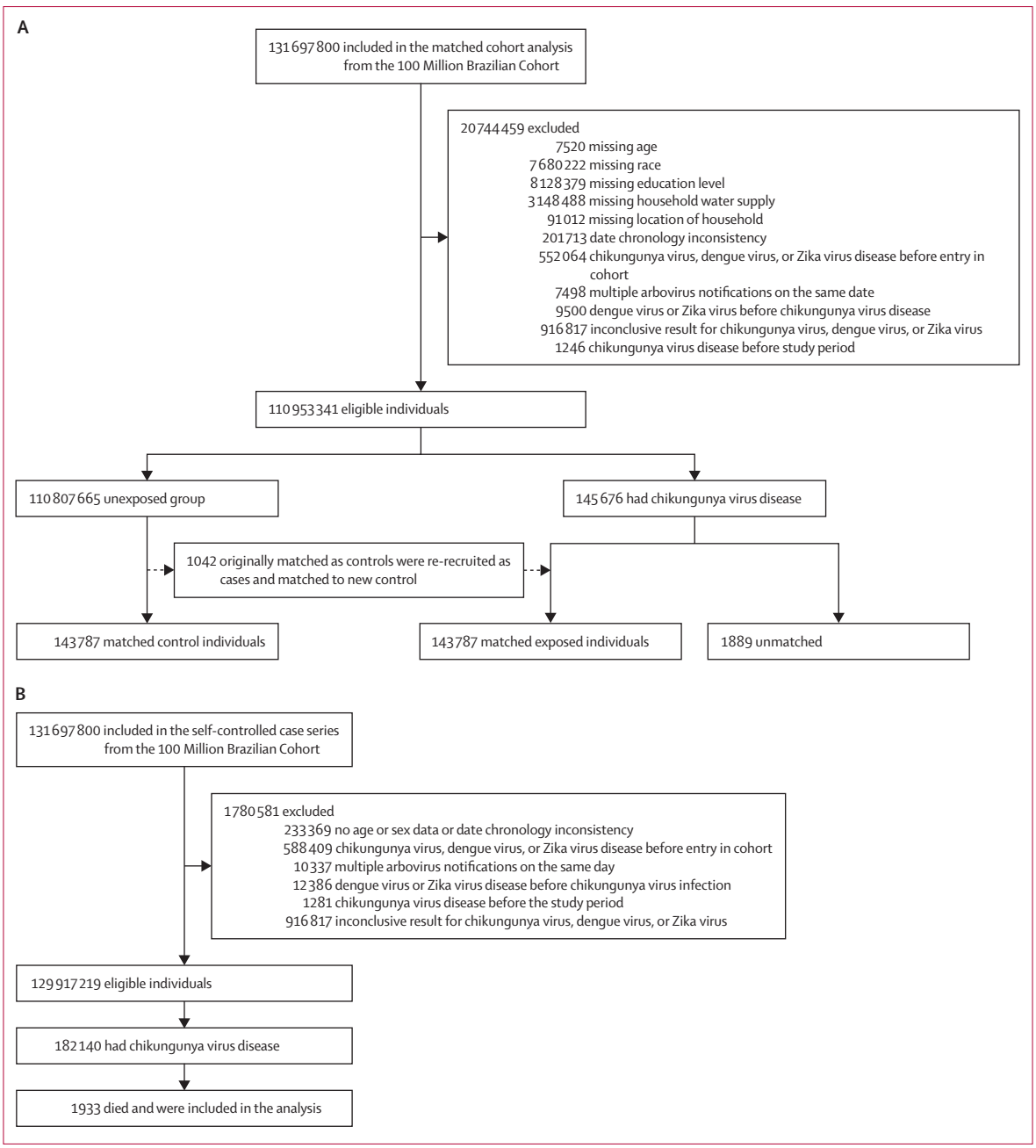

Figure 1: **Selection process for the (A) matched cohort study and (B) self-controlled case series study**
Individuals were excluded sequentially according to the exclusion criteria. Detailed information on chikungunya virus disease cases with missing data can be found in appendix 2 (pp 4–5).

We included all deaths from individuals with a chikungunya virus disease record between Jan 1, 2015, and Dec 31, 2018. We excluded individuals with missing data on age or sex, those who had dengue or Zika virus co-infections recorded on the same day as the onset of symptoms of chikungunya virus disease, and individuals for whom there was inconsistency in the date chronology. Appendix 2 (pp 5–7) shows details on the self-controlled case series and exclusion criteria.

The self-controlled case series method uses conditional Poisson regression to compare intra-person mortality rates in different study periods relative to the date of disease onset. For each mortality outcome, we compared the mortality rate in the 0–168 days following the symptom onset of chikungunya virus disease to the mortality rate in the period defined as the baseline (from 169th day after symptom onset until Dec 31, 2018). Therefore, we included only post-disease person-time

during the 4-year study period, necessary to meet assumptions of self-controlled case series when the outcome is death. We also evaluated the period-specific risk of death during the following time windows: 0, 1–7, 8–14, 15–28, 29–56, 57–84, and 85–168 days. Due to the reduced sample size for specific causes of death, the period-specific risk of the secondary outcomes was evaluated during only the following time windows: 0, 1–28, 29–56, 57–84, and 85–168 days. We did not estimate IRRs for risk periods with two or fewer cases. We used likelihood ratio tests to investigate heterogeneity between subgroups, sex (female, male) and age (<60, ≥60 years).[3] All data processing and analyses were done in R (version 4.1.1), using the packages tidyverse, SCCS, and survival.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Matched cohort design

Among the 110 953 341 eligible people who were followed up in the 100 Million Brazilian Cohort, 145 676 had chikungunya virus disease and were eligible for matching. Among these, 32 509 (22·3%) were laboratory-confirmed cases. A total of 143 787 (98·7%) were matched with an unexposed individual (figure 1A and table 1). Compared with matched individuals, the unmatched individuals (1889 [1·3%]) were older (median 36 years [IQR 23–52] *vs* 23 years [10–38]), more educated, and more likely to be of Asian and indigenous race or ethnicities (appendix 2 p 8). A total of 1042 people initially matched as controls were re-recruited as cases and matched to a new control. The median follow-up period was 630 days (IQR 553–728) and was similar between groups as the censoring occurred by pairs (appendix 2 p 9). During the study period, 2282 deaths were registered, 1269 in the chikungunya virus-exposed group and 1013 in the control group.

During the first week after symptom onset, the RR of all-cause natural death in the chikungunya virus-exposed group compared with the unexposed group was 8·42 (95% CI 4·85–20·18). The RR decreased to 3·00 (95% CI 2·46–3·72) at 57–84 days and to 1·26 (1·15–1·38) at 365–728 days (table 2, appendix 2 p 22). The risk difference comparing chikungunya virus-exposed individuals versus unexposed individuals increased over time, peaking at 728 days with 192·01 (95% CI 115·96–261·71) more deaths per 100 000 people in the chikungunya virus-exposed group (table 2, appendix 2 p 22).

The IRR for all-cause natural death comparing chikungunya virus-exposed individuals with unexposed individuals decreased from 8·40 (95% CI 4·83–20·09) at 1–7 days to 1·05 (0·82–1·35) at 85–168 days. In the subsequent periods, the IRR presented values close to 1 with 95% CIs crossing 1 (table 2).

	Matched cohort		Self-controlled case series (n=1933)
	Chikungunya virus disease (n=143 787)	Control (n=143 787)	
Median age, years	23 (10–38)	23 (10–38)	62 (44–74)
Sex			
Female	91 787 (63·8%)	91 787 (63·8%)	1024 (53·0%)
Male	52 000 (36·2%)	52 000 (36·2%)	909 (47·0%)
Water System			
Public system	108 517 (75·5%)	108 517 (75·5%)	1414 (76·0%)
Water well	23 081 (16·1%)	23 081 (16·1%)	266 (14·3%)
Other	12 189 (8·5%)	12 189 (8·5%)	182 (9·8%)
Missing	..	..	71
Garbage disposal			
Public collection system	117 190 (81·5%)	116 078 (80·7%)	1529 (82·1%)
Burned	16 591 (11·5%)	17 529 (12·2%)	190 (10·2%)
Open air dump	8407 (5·8%)	8630 (6·0%)	123 (6·6%)
Other	1596 (1·1%)	1548 (1·1%)	20 (1·1%)
Missing	3	2	71
Location of household			
Urban	120 184 (83·6%)	120 184 (83·6%)	1562 (80·8%)
Rural	23 603 (16·4%)	23 603 (16·4%)	321 (16·6%)
Geographical region			
North	9247 (6·4%)	9247 (6·4%)	73 (3·8%)
Northeast	105 255 (73·2%)	105 255 (73·2%)	1603 (82·9%)
Southeast	22 992 (16·0%)	22 992 (16·0%)	203 (10·5%)
South	175 (0·1%)	175 (0·1%)	3 (0·2%)
Central-west	6118 (4·3%)	6118 (4·3%)	47 (2·4%)
Race			
White	27 740 (19·3%)	27 740 (19·3%)	312 (17·6%)
Black	8462 (5·9%)	8462 (5·9%)	144 (8·1%)
Mixed	106 748 (74·2%)	106 748 (74·2%)	1306 (73·5%)
Asian	403 (0·3%)	403 (0·3%)	9 (0·5%)
Indigenous	434 (0·3%)	434 (0·3%)	5 (0·3%)
Missing	..	..	157
Education level			
No school	32 658 (22·7%)	32 658 (22·7%)	584 (34·4%)
Pre-school	4542 (3·2%)	4542 (3·2%)	39 (2·3%)
Literate	2712 (1·9%)	2712 (1·9%)	11 (0·6%)
Elementary school up to 5 years of schooling	44 555 (31·0%)	44 555 (31·0%)	674 (39·6%)
Elementary school 6–9 years of schooling	36 792 (25·6%)	36 792 (25·6%)	263 (15·5%)
High School	21 173 (14·7%)	21 173 (14·7%)	123 (7·2%)
College	1355 (0·9%)	1355 (0·9%)	6 (0·4%)
Missing	..	..	233
Ever received conditional cash transfer (yes)	121 516 (84·5%)	117 912 (82·0%)	1344 (69·5%)
Deaths	1269 (0·9%)	1013 (0·7%)	1933 (100%)

Data are n (%) or median (IQR).

Table 1: **Baseline characteristics of people included in the cohort and self-controlled case series analyses**

Regarding specific causes of death, the risk of mortality due to diabetes and ischaemic heart disease increased in the first 28 days after chikungunya virus

	Number of natural deaths*		Risk per 100 000 people (95% CI)		Risk difference per 100 000 people (95% CI)	Risk ratio (95% CI)	Incidence rate ratio (95% CI)
	Unexposed control group	Chikungunya virus-exposed group	Unexposed control group	Chikungunya virus-exposed group			
1–7 days	10	84	6·97 (2·80–11·84)	58·73 (44·74–71·99)	51·75 (36·40–65·06)	8·42 (4·85–20·18)	8·40 (4·83–20·09)
8–14 days	10	64	14·00 (8·40–20·33)	103·68 (85·11–120·88)	89·68 (69·36–109·26)	7·41 (4·82–12·42)	6·40 (3·43–14·00)
15–28 days	21	69	28·84 (19·72–37·31)	152·39 (132·05–171·06)	123·55 (102·46–146·33)	5·28 (3·92–7·66)	3·29 (2·18–5·73)
29–56 days	52	84	65·87 (51·70–78·34)	212·10 (189·20–235·29)	146·23 (119·42–172·18)	3·22 (2·58–4·13)	1·62 (1·12–2·32)
57–84 days	27	61	85·24 (69·95–99·84)	255·79 (229·02–281·54)	170·56 (140·14–200·19)	3·00 (2·46–3·72)	2·26 (1·50–3·77)
85–168 days	111	117	165·96 (144·43–185·37)	340·72 (310·04–369·33)	174·76 (137·96–209·82)	2·05 (1·75–2·40)	1·05 (0·82–1·35)
169–364 days	256	230	369·32 (336·60–401·14)	522·47 (483·39–557·74)	153·15 (95·98–199·59)	1·41 (1·25–1·59)	0·90 (0·75–1·07)
365–728 days	341	381	731·18 (681·42–779·26)	923·19 (865·04–971·06)	192·01 (115·96–261·71)	1·26 (1·15–1·38)	1·12 (0·97–1·27)

*11 pairs were excluded because the death occurred on day 0 of follow-up.

Table 2: **Estimated risk for all-cause natural death in the chikungunya virus-exposed group compared with the unexposed group, by risk period**

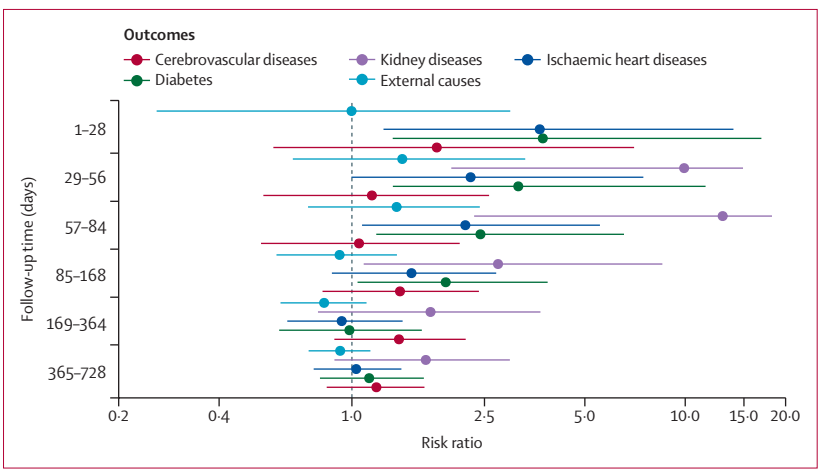

Figure 2: **Estimated risk ratios for deaths due to specific causes, comparing groups exposed and unexposed to chikungunya virus disease in each risk period**

The risk ratio for kidney diseases within 28 days of symptom onset could not be estimated because there were no events in the unexposed group. Deaths due to external causes, which are not causally associated with chikungunya virus disease, were used as an outcome-negative control.[18] The x axis is plotted on a logarithmic scale.

disease (RR 3·74, 95% CI 1·33–16·93, for diabetes, and 3·66, 1·25–13·96, for ischaemic heart disease) and remained significantly elevated up to 168 days for diabetes and up to 84 days for ischaemic heart disease, after which the 95% CIs for RR crossed 1. For cerebrovascular diseases, we found an elevated RR but with wide CIs that crossed 1 for all time periods (eg, RR 1·80, 95% CI 0·58–7·03, in the first 28 days). A comparison between IRR and RR revealed similar values up to 28 days after the onset of the symptoms of chikungunya virus disease for all specific causes of death. After this period, the IRRs showed no evidence of increased risk of mortality in the exposed group compared with the control group for cause-specific deaths (appendix 2 p 10). For kidney disease, due to a low number of events, only the RR at 85–168 days could be estimated precisely (2·75, 95% CI 1·09–8·54; figure 2, appendix 2 p 10).

Chikungunya virus disease presented different effects on the risk of all-cause natural death by age group and sex. The effect modification on the additive scale (risk difference scale) of chikungunya virus disease by age group was 21·29 (95% CI 12·45–35·01), meaning that the combined effect of chikungunya virus disease and age group (age ≥60 years) was 21·29 more than the expected effect if there was no interaction between chikungunya virus disease and age group. The measure of interaction on the multiplicative scale (relative measure of association), was 0·42 (95% CI 0·26–0·66), indicating that the relative effect of chikungunya virus disease in individuals aged 60 years or older was smaller than the estimated effect of chikungunya virus disease in younger individuals (appendix 2 pp 11, 23). In the case of sex, the effect modification on the additive scale was 1·89 (95% CI 1·67–2·85) and on the multiplicative was 1·72 (1·13–2·74), showing that the effect of chikungunya virus disease in male individuals was larger than in the female individuals in both scales (appendix 2 pp 11, 23).

The outcome-negative control analysis (deaths due to external causes) showed little evidence of large residual confounding. The RR of death between the chikungunya virus-exposed group and the unexposed group in all periods following chikungunya virus disease ranged from 0·83 (95% CI 0·61–1·11) at 169–364 days to 1·42 (0·67–3·31) at 29–56 days, with wide CIs in each risk period (figure 2, appendix 2 p 10).

In the sensitivity analysis using only cases of chikungunya virus disease confirmed by a laboratory test, the same pattern was noted, but with imprecise estimates due to sample size reduction. The IRR of all-cause natural deaths comparing chikungunya virus-exposed individuals with unexposed individuals decreased from 9·50 (95% CI 4·54–45·65) at 1–14 days to 1·26 (0·74–2·12) at 85–168 days, and to 1·00 (0·68–1·44) at 169–364 days and 0·93 (0·69–1·32) at 365–728 days (appendix 2 p 12). The results excluding education level

or race or ethnicity from the matching criteria remained consistent with the main analysis (appendix 2 pp 13,14).

Self-controlled case series design

Between 2015 and 2018, 182 140 individuals from the 100 Million Brazilian Cohort were notified as cases of chikungunya virus disease, of whom 1933 died, with a median time between disease and death of 294 days (IQR 67–546; figure 1B). The median age of the individuals who died after chikungunya virus disease was 62 years (44–74), and 1024 (53·0%) were female (table 1, appendix 2 pp 19,24). 545 (28·2%) deaths occurred in the first 12 weeks after chikungunya virus disease. The leading cause of death in all periods was ischaemic heart disease (n=159; 8·2%), followed by cerebrovascular disease (n=126; 6·5%), and 113 (5·8%) deaths were due to arthropod-borne viral fevers (appendix 2 p 15).

Similar to the cohort analysis, the self-controlled case series analysis showed an increased relative risk of all-cause natural mortality within 84 days after symptom onset. Within the first week, the IRR was 8·75 (95% CI 7·18–10·66), and it remained elevated 57–84 days after disease onset (1·59, 1·26–2·00). In the last period (85–168 days), the IRR was 1·09 (0·92–1·29). The overall IRR 1–84 days after symptom onset was 3·23 (2·89–3·61; table 3).

In the first 28 days after chikungunya virus disease, there was an increase in mortality for cerebrovascular diseases (IRR 2·73, 95% CI 1·50–4·96), diabetes (8·43, 5·00–14·21), ischaemic heart disease (2·38, 1·33–4·26), and kidney disease (8·53, 3·65–19·94). The IRRs of all four outcomes were close to 1, with wide CIs, at 85–168 days after disease onset (figure 3, appendix 2 p 20).

In our negative-outcome analysis, evaluating the association between chikungunya virus disease and death due to external causes, we found evidence of little residual confounding with an IRR of 1·11 (95% CI 0·76–1·62) in 1–84 days, and similar values in all other risk periods (figure 3, appendix 2 p 20).

There was evidence of effect heterogeneity for sex (p=0·014) and age (p=0·012). The overall IRR in 1–84 days was 3·88 (95% CI 3·29–4·58) for male individuals and 2·77 (2·38–3·23) for female individuals (appendix 2 p 25). In the same risk period, the IRR was 4·16 (3·49–4·94) for individuals younger than 60 years and 2·72 (2·35–3·15) for those aged 60 years or older (appendix 2 p 26).

In the sensitivity analysis using only laboratory-confirmed cases of chikungunya virus disease (n=405 deaths, 24·0%), we found initially larger effects; however, we also observed the same pattern of decreasing risk over time (table 3).

	Overall cases of chikungunya virus disease (1684 all-cause natural deaths)		Laboratory-confirmed cases of chikungunya virus disease (405 all-cause natural deaths)	
	Number of deaths (%)	IRR (95% CI)	Number of deaths (%)	IRR (95% CI)
Control	1010 (60·0%)	..	170 (42·0%)	..
0 days	16 (1·0%)	8·75 (5·33–14·35)	7 (1·7%)	19·50 (9·13–41·62)
1–84 days	495 (29·4%)	3·23 (2·89–3·61)	187 (46·2%)	6·22 (5·01–7·72)
1–7 days	112 (6·7%)	8·75 (7·18–10·66)	34 (8·4%)	13·53 (9·31–19·65)
8–14 days	86 (5·1%)	6·72 (5·38–8·39)	41 (10·1%)	16·31 (11·54–23·07)
15–28 days	93 (5·5%)	3·63 (2·93–4·50)	37 (9·1%)	7·36 (5·13–10·56)
29–56 days	123 (7·3%)	2·41 (1·99–2·91)	45 (11·1%)	4·51 (3·23–6·29)
57–84 days	81 (4·8%)	1·59 (1·26–2·00)	30 (7·4%)	3·01 (2·03–4·45)
85–168 days	163 (9·7%)	1·09 (0·92–1·29)	41 (10·1%)	1·42 (1·00–2·00)

IRR=incidence rate ratio.

Table 3: **IRRs of all-cause natural death following chikungunya virus disease in overall cases and in laboratory-confirmed cases, by risk period**

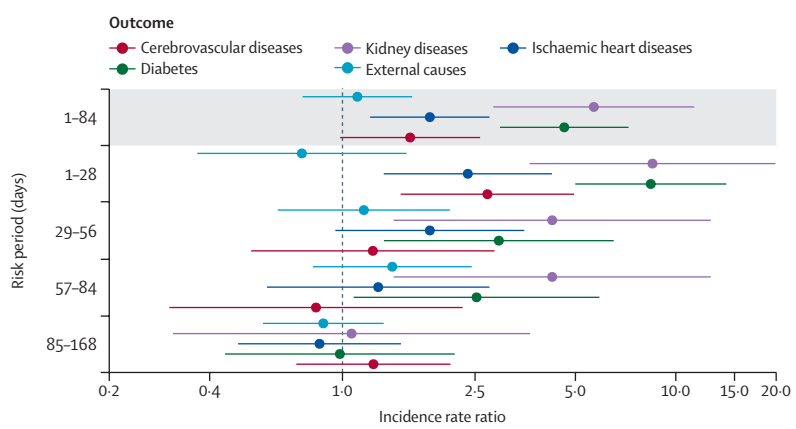

Figure 3: **Estimated incidence rate ratios for deaths due to specific causes by risk period from the self-controlled case series**

Deaths due to external causes, which are not causally associated with chikungunya virus disease, were used as an outcome-negative control.[18] The x axis is plotted on a logarithmic scale.

Discussion

The evidence from this nationwide registry-based cohort in Brazil suggests chikungunya virus disease is associated with an increased risk of all-cause natural mortality, as well as an increased risk of death from cerebrovascular disease, ischaemic heart disease, diabetes, and kidney disease, within 84 days of symptom onset. Similar results were obtained using two methodological approaches: a matched cohort and a self-controlled case series. The validity and reliability of the results were supported by a lack of increased risk of death in the negative-outcome analysis (which was restricted to deaths due to external causes) and the similarity of findings in the sensitivity analysis (which included only laboratory-confirmed cases of chikungunya virus disease). The elevated mortality following chikungunya virus disease adds to the known risks posed by *Aedes* mosquito-borne diseases,[19] which are anticipated to increase in frequency due to climate change, urbanisation, and heightened human mobility.

Currently, due to the small number of comprehensive studies, the WHO chikungunya clinical management

guideline does not contain risk factors and alert signals for severe chikungunya virus disease.[20] According to a systematic review of global guidelines for chikungunya clinical management from 2022, only 35% of the guidelines provided a definition of severe chikungunya virus disease that included atypical manifestations (ie, non-musculoskeletal), highlighting the need for more comprehensive and effective guidelines.[3] The increased risk of mortality across age groups reinforces the need for health-care providers to closely monitor cases for cardiovascular, neurological, renal, and metabolic disorders, and other severe clinical manifestations linked to systemic ailments and organ-specific involvement,[21] enabling the early detection and prevention of complications and deaths.

It is worth noting that chikungunya virus disease can exacerbate underlying diseases. One study from Puerto Rico, which evaluated 27 fatal cases following chikungunya virus disease, showed at least one medical comorbidity in 93% of the cases, and viral antigen was present in multiple organs, such as the kidneys, lungs, and heart.[22] Similarly, in Brazil, a study of 42 autopsies of individuals previously diagnosed with chikungunya virus disease revealed organ dysfunction, particularly in the lungs and heart, attributed to haemodynamic disturbances.[23] These studies suggest that chikungunya virus can potentially decompensate multiple chronic diseases. Regarding the risk of ischaemic heart diseases, previous self-controlled case series studies reported similar findings to our study in other viral diseases; 1 week after dengue virus disease onset, the IRR for hospitalisation due to myocardial infarction was 13·53 (95% CI 10·13–18·06), and the IRR for hospitalisation due to myocardial infarction for influenza virus 1 week after onset of influenza was 6·05 (95% CI 3·86–9·50).[8,24] Consistent with these observations, in the self-controlled case series approach we found a two-fold increase in IRR for death due to any ischaemic heart disease within the first 28 days of symptom onset of chikungunya virus disease. Acute viral infections can trigger systemic inflammation, which can trigger thrombus formation, exacerbate endothelial dysfunction, and hasten the onset of ischaemic heart diseases.[25] The increased risk of mortality due to diabetes after chikungunya virus disease might result from metabolic changes caused by the infection. A significant increase in glycaemic levels was observed in 46 patients with diabetes within the first week after chikungunya virus infection.[26] The hyperglycaemic state can induce an inflammatory response and promote endothelial dysfunction, reducing blood flow and increasing the risk of vascular disease.[27,28] Further studies should evaluate the mechanisms underlying the interconnection of chikungunya virus disease and worse outcomes in individuals with chronic inflammatory diseases.

We found effect modification by sex and age of chikungunya virus disease on both additive and multiplicative scales. For age group, we found a positive additive and negative multiplicative interaction, with the individuals aged 60 years or older presenting higher absolute risks and lower relative risks than individuals younger than 60 years. This discrepancy could have arisen because of the higher baseline mortality risks in older individuals than in younger ones. In this context, the relative increase in deaths due to chikungunya virus disease is less pronounced in older individuals than in younger ones. Regarding sex, both additive and multiplicative interactions revealed increased mortality risk in male individuals, and this pattern remained consistent in the self-controlled case series analysis, which implicitly controlled for sex-based differences in health-seeking behaviour. This difference in mortality between sexes has been seen in other conditions, such as COVID-19 and sepsis,[29,30] suggesting that shared mechanisms are probably responsible for worse outcomes in male individuals.

A strength of our study is the large sample, which includes all confirmed and probable cases of chikungunya virus disease identified in the nationwide 100 Million Brazilian Cohort between Jan 1, 2007, and Dec 31, 2018. This robust sample size, coupled with the triangulation of two distinct methodologies yielding similar results, enhances the reliability of our findings. Additionally, the subgroup analysis by age and sex presented consistent patterns across strata, which extends the generalisability of our findings to other populations, particularly to those in other lower-income and middle-income countries with similar demographic profiles.

To proactively address known limitations of observational studies, we used complementary approaches with different assumptions, control strategies, and sources of bias. In the cohort analysis, bias was primarily due to residual confounding from unmatched differences in socioeconomic characteristics and unmeasured confounders. In the self-controlled case series, bias was primarily due to time-varying confounding, such as seasonal effects. However, we acknowledge that misclassification of exposure can occur in both methodologies. Another limitation in the matched cohort study was the missing data in the variables used for matching. Additionally, we did not have information regarding medical comorbidities, which are recognised as risk factors for mortality. However, in our directed acyclic graph (appendix 2 p 21), we considered that the likely role of comorbidities was as mediators of the effect of chikungunya virus disease and, therefore, they should not be adjusted for. In this scenario, we estimated the total effect of chikungunya virus disease on death. Furthermore, the outcome-negative control analysis suggested little residual confounding in both study designs. Another limitation arose in the secondary outcome analysis, in which some risk periods had a low number of events, resulting in imprecise estimates.[31] Additionally, we cannot rule out

exposure misclassification, as only 24% of cases were laboratory-confirmed. Furthermore, as exposures were based on notification records, we could only assess the risk after symptomatic chikungunya virus infection; however, it is reported that only 3–28% of chikungunya virus infections are asymptomatic.[32] Finally, we acknowledge that our study period includes a period of fiscal austerity in Brazil, with large funding cuts for the Brazilian Unified Health System (SUS).[33] This austerity might have diminished SUS's capacity to respond to chikungunya virus outbreaks, consequently contributing to the increased burden of chikungunya virus disease in the country.

Our research has important clinical and epidemiological implications and can inform intersectoral actions to reduce the negative impacts of neglected tropical diseases in affected populations, as agreed in the Sustainable Development Goals 2030 Agenda.[34] It is important that national and international guidelines highlight the potential increased risk of death after chikungunya virus disease that persists after the acute phase. It is essential for health-care professionals to acknowledge the potential complications of chikungunya virus disease, which can contribute to reducing mortality. Our research also highlights the need for continued research and development of effective drugs and immunotherapies against chikungunya virus, and for ensuring equitable access to affordable vaccines in countries with recurrent outbreaks as early as they become approved.[5] Furthermore, reinforcing measures to control the spread of mosquitoes carrying chikungunya virus is also essential for reducing the excess mortality associated with the disease.

Contributors

TC-S wrote the first draft of manuscript. TC-S, JMP, ESP, and VSB conceptualised the study. TC-S curated the data. HW and CL supervised the data analysis. TC-S conducted the formal analysis. All authors contributed to writing, reviewing, and editing of the manuscript. TC-S decided to submit the manuscript for publication. TC-S and ESP had access to the raw data in the study and accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

The relevant data are available in the manuscript and the appendix. Raw data are available upon reasonable request to the Centro de Integração de Dados e Conhecimentos para a Saúde (CIDACS). Any person who wishes to receive authorisation must: (1) be affiliated to CIDACS or be accepted as collaborators; (2) present a detailed research project together with approval by an appropriate Brazilian institutional research ethics committee; (3) provide a clear data plan restricted to the objectives of the proposed study and a summary of the analyses plan intended to guide the linkage and data extraction of the relevant set of records and variables; (4) sign terms of responsibility regarding the access and use of data; and (5) perform the analyses of datasets provided using the CIDACS data environment, a safe and secure infrastructure that provides remote access to de-identified or anonymised datasets and analysis tools. For more information: https://cidacs.bahia.fiocruz.br/

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