CLINICAL INVESTIGATION

Acetaminophen Safety: Risk of Mortality and Cardiovascular Events in Nursing Home Residents, a Prospective Study

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BACKGROUND: Acetaminophen is the most widely used analgesic today. A recent systematic review found increased adverse events and mortality at therapeutic dosage. Our aim was to challenge these results in a large sample of older adults living in nursing homes (NHs).

DESIGN: Prospective study using data from the Impact of Educational and Professional Supportive Interventions on Nursing Home Quality Indicators project (IQUARE), a multicenter, individually tailored, nonrandomized controlled trial in NHs across southwestern France.

SETTING/PARTICIPANTS: We studied data from 5429 participants living in 175 NHs (average age, 86.1 ± 8.1 years; 73.9% women).

MEASUREMENTS: All prescriptions obtained at baseline were analyzed by a pharmacist for acetaminophen use as stand-alone or associated. Myocardial infarction (MI) and strokes were reported from participants' medical records at 18-month follow-up. Dates of death were obtained. Data collection was done through an online questionnaire at baseline and at 18 months by NH staff. Analyses were realized in our total population and a population matched on propensity score of acetaminophen intake. Six models were run for each outcome.

RESULTS: A total of 2239 participants were taking, on average, 2352 ± 993 mg of acetaminophen daily. Results for mortality were: hazard ratio (HR) = 0.97 (95% confidence interval [CI] = 0.86-1.10). No associations between acetaminophen intake and the risk of mortality or MI were found. In one of our models, acetaminophen intake was associated with a significant increased risk of stroke in diabetic subjects (HR = 3.19; 95% CI = 1.25-8.18; *P* = .0157).

CONCLUSION: Despite old age, polypharmacy, and polymorbidity, acetaminophen was found safe for most, but not all, of our NH study population. Pain management in NHs is a health priority, and acetaminophen remains a good therapeutic choice as a first-line analgesic. More studies are needed on older diabetic patients. **J Am Geriatr Soc 00:1–8, 2019.**

Key words: acetaminophen safety; nursing home; geriatric; pain management; propensity score

Acetaminophen is one of the most widely used analgesic drugs today.[1] Almost 60 years of widespread use have made it a household product, distributed over the counter in most countries and judged safe by the scientific community at large.[2] It is also one of the most commonly overdosed drugs and the most common cause for drug-induced hepatic failure.[3] Surprisingly, its pharmacological mechanisms of action, which can explain some of its adverse effects, are only recently being discovered.[4]

Studies have suggested its harmlessness may have been overestimated.[5] Reports showing the associations of acetaminophen consumption with increased asthma,[6] renal toxicity,[7] increased attention-deficit/hyperactivity disorder in children,[8] increased risk of bone fracture,[9] increased hematologic malignancy,[10] and interactions with other drugs, such as warfarin,[11] have highlighted the need for caution in its use. Plainly, even a rare or small adverse effect may become clinically significant in such a widely used drug. The recent systematic review by Roberts et al,[12] which found increased cardiovascular adverse events (AEs) and gastrointestinal AEs associated with the use of acetaminophen at therapeutic dose ranges, brought it under the scientific community's scrutiny once more in 2015. Since then, these results have been challenged,[13,14] given the observational nature of the data, the quality of the studies being

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reviewed, and the many confounding factors, from subjects' medical history to concomitant drug use.

Compared to adults, older adults are characterized by lower physiological reserves and changes in body composition (augmented fat tissue, diminished muscle mass, and diminished hydration), altered enzymatic function, kidney failure, polymorbidity, and polypharmacy, leading to an increased risk of AEs. Studying the safety of acetaminophen use in a nursing home (NH) setting, whence the oldest people reside, should bring potential harmful effects to full light. Older adults are also the group with the highest use of analgesic drugs,[15] and despite this, the safety of acetaminophen in this population has been poorly investigated. Our aim was to explore the association of acetaminophen usage with mortality and major cardiovascular events (strokes and myocardial infarction [MI]) in a large sample of older adults living in NHs.

METHODS

We performed a secondary analysis of the data from the Impact of Educational and Professional Supportive Interventions on Nursing Home Quality Indicators (IQUARE) study, a multicenter, individually tailored, nonrandomized controlled trial developed in NHs in southwestern France (trial registration NCT01703689). The study comprised a 6-month intervention period and an 18-month follow-up, and it was designed to improve NH quality indicators related to frequent medical problems faced by NH staff. The full protocol[16] and final results have been described elsewhere.[17] IQUARE followed the principles of the Declaration of Helsinki and complied with ethical standards in France; study protocol was approved by the ethics committee of the Toulouse University Hospital and the Consultative Committee for the Treatment of Research Information on Health (commission nationale de l'informatique et des libertés [CNIL]: 07-438).

Participants

A total of 6275 residents from 175 NHs were included at baseline in IQUARE. Information on NH residents' health status was recorded by NH staff. Our main outcome study population was 5429 subjects (Table 1 provides population characteristics, and Figure 1 shows a flowchart).

Procedure

Data for the IQUARE study were collected through two different questionnaires, completed online by the NH staff: a questionnaire about the NH structure and internal organization that was completed by the NH administrative staff; and another questionnaire that collected information on residents' health status, which was completed by the NH medical staff, mainly the coordinating physician.

With regard to medications, the NH staff sent to the IQUARE research team all drug prescriptions that participants were taking in the week they were included in the study.

Data collection for the prescription of acetaminophen at inclusion (dosage in milligrams) was done by a pharmacist who researched all prescriptions of acetaminophen either as a stand-alone or associated with other molecules; "on-demand" prescriptions were excluded.

Outcome

The main outcome was mortality during the 18-month follow-up. Residents' exact date of death was recorded through the online questionnaire.

Secondary outcomes were stroke and MI during the 18-month follow-up. The occurrence of new diagnoses of stroke or MI was recorded by coordinating physicians through the online questionnaire as part of the Charlson Comorbidity Index,[18] according to residents' medical records at 18-month follow-up. The date of the event was unknown in both cases.

Acetaminophen

Acetaminophen alone or associated was coded using the Anatomical Therapeutic Chemical classification.

Binary variable acetaminophen was used in main and secondary outcome statistical calculations.

Acetaminophen dosage was in milligrams per day, organized into range subgroups (100-1000, 1000-2000, 2000-3000, and 3000 mg or more) for discrete variable statistical analyses.

Confounders

All confounders were recorded in the online questionnaire at baseline, based on subjects' medical records. Table 1 and Supplementary Material S7 provide a listing of cofounders.

Statistical Analysis

To study the effect of acetaminophen use on mortality (primary outcome) and the incidence of MI and stroke (secondary outcomes) at 18 months, we excluded subjects with missing doses or subjects with acetaminophen prescribed on demand.

Baseline characteristics were summarized as mean ± SD for continuous variables and as frequencies and percentages for other variables.

To compare the baseline characteristics in regard to acetaminophen prescription, we used Kruskal-Wallis tests for quantitative variables (because of their nongaussian distribution), χ^2 tests for qualitative variables, or Fisher's exact test if there was an expected frequency of less than five.

Since the use of acetaminophen was not randomly assigned in this study population, propensity scores[19,20] were calculated to account for potentially confounding factors for each outcome. This technique allowed us to approach a randomized trial in terms of bias. Supplementary Material S7 provides the detailed calculation of our propensity scores.

First, we used a multivariate logistic regression to determine the factors independently associated with acetaminophen intake at baseline (Supplementary Material S7 provides details).

Next, we designed a cohort study matched by propensity score from the previous logistic model with a greedy match algorithm (the SAS Greedy 5 → 1 digit match macro).[21] Subjects who received acetaminophen were matched to subjects who did not.

To check the quality of the match, we compared the baseline characteristics and the means of propensity scores by decile (with a *t*-test) between the two groups of acetaminophen

Table 1. Population Characteristics at Inclusion

Characteristics	With Acetaminophen (n = 2239)	Without Acetaminophen (n = 3190)	*P* Value	*P* Value[a]
Age, mean ± SD, y	87.0 ± 7.5	85.4 ± 8.4	<.001	.967
Sex, No. (%)			<.001	.845
Women	1752 (78.3)	2258 (70.8)		
Men	487 (21.7)	932 (29.2)		
Place of previous residence before NH, No. (%)			.011	.064
Home	1126 (53.3)	1716 (57.6)		
Hospital ward	757 (35.8)	977 (32.8)		
Other NH	229 (10.8)	289 (9.7)		
Length of stay in NH, mean ± SD, mo	48.6 ± 52.8	54.3 ± 57.5	<.001	.479
Autonomy, GIR, mean ± SD	2.9 ± 1.4	2.7 ± 1.5	<.001	.591
Medical record/comorbidities				
Myocardial infarction, No. (%)	162 (7.2)	237 (7.4)	.787	.055
Peripheral vascular disease, No. (%)	436 (19.5)	538 (16.9)	.014	.829
Cardiac insufficiency, No. (%)	452 (20.2)	614 (19.3)	.391	.001
Hypertension, No. (%)	1273 (56.9)	1610 (50.5)	<.001	.570
Hemiplegia, No. (%)	106 (4.7)	129 (4.0)	.219	.628
Stroke, except hemiplegia, No. (%)	301 (13.4)	408 (12.8)	.482	.047
Diabetes, No. (%)	334 (14.9)	528 (16.6)	.105	.578
Chronic pulmonary disease, No. (%)	248 (11.1)	317 (9.9)	.176	.489
AIDS, No. (%)	2 (0.1)	1 (0.0)	.573	1.000
Peptic ulcer, No. (%)	124 (5.5)	157 (4.9)	.313	.878
Hepatic disease (mild), No. (%)	26 (1.2)	39 (1.2)	.838	.878
Hepatic disease (moderate to severe), No. (%)	30 (1.3)	41 (1.3)	.862	.569
Renal insufficiency (moderate to severe), No. (%)	278 (12.4)	366 (11.5)	.290	.141
Epilepsy, No. (%)	99 (4.4)	157 (4.9)	.392	.681
Cancer/malignant blood disease, No. (%)	301 (13.4)	377 (11.8)	.075	.882
Connective tissue disease, No. (%)	30 (1.3)	71 (2.2)	.017	.666
Dementia, No. (%)	802 (36.2)	1475 (46.8)	<.001	.368
Depression, No. (%)	825 (37.2)	1011 (32.0)	<.001	.737
Psychiatric disease, except depression, No. (%)	328 (14.7)	651 (20.5)	<.001	.885
Charlson index, mean ± SD	2.0 ± 1.8	2.1 ± 1.8	.532	.362
Fracture(s), No. (%)	1051 (48.6)	1040 (34.3)	<.001	.643
Falls in the previous year, No. (%)	1067 (48.2)	1222 (39.0)	<.001	.615
Hospitalization within the prior year, No. (%)	754 (34.8)	912 (29.3)	<.001	.503
Bedsores, No. (%)	97 (4.4)	116 (3.6)	.187	.952
Pain/palliative care, No. (%)				
Verbal, visual, numerical, or behavioral validated pain scale	337 (15.1)	235 (7.4)	<.001	.715
Pain complaint	833 (37.5)	442 (14.0)	<.001	.399
Treatments				
No. of medications, mean ± SD	8.2 ± 3.3	6.9 ± 3.3	<.001	.293
Opiates, No. (%)	96 (4.3)	105 (3.3)	.056	.029

Abbreviations: AIDS, acquired immune deficiency syndrome; NH, nursing home.
[a]*P* value after propensity score matching.

intake. We found no significant difference for the factors that were independently associated with acetaminophen intake at baseline in the whole population and for each decile of propensity score between the two groups (Tables 1 and 2).

Finally, we performed six models for each outcome with the binary variable acetaminophen prescription (yes/no). First, there were four models in the total population: an unadjusted model (M1); a second model (M2) with adjustments on covariates independently associated with acetaminophen intake at baseline; a third model (M3) with adjustments on propensity score by decile; and a fourth model (M4) with adjustments on propensity score, excluding the decile(s) that were significantly different between the two groups of acetaminophen intake. Then, there were two more models in the matched cohort study: an unadjusted model (M5) and an adjusted model (M6) with the parameters becoming significantly different between the two groups after matching. We performed the same models with acetaminophen dosage in milligrams per day organized into range subgroups. In the models M2 and M6 adjusted on covariates, we tested the interactions between acetaminophen and each covariate.

To study mortality, we used Cox proportional hazard models with their hazard ratios (HRs) and 95% confidence intervals (95% CIs). We defined time to event as the time between the date of baseline and the date of death from any cause or the date of the last follow-up for other subjects. Survival curves were plotted with the Kaplan-Meier method (Figure S6). The follow-up planned for this study was 18 months; for this survival analysis, we took as the end date of follow-up 18 + 2 months.

For each model, tests based on interaction with time were used to assert the proportional hazards assumption for the

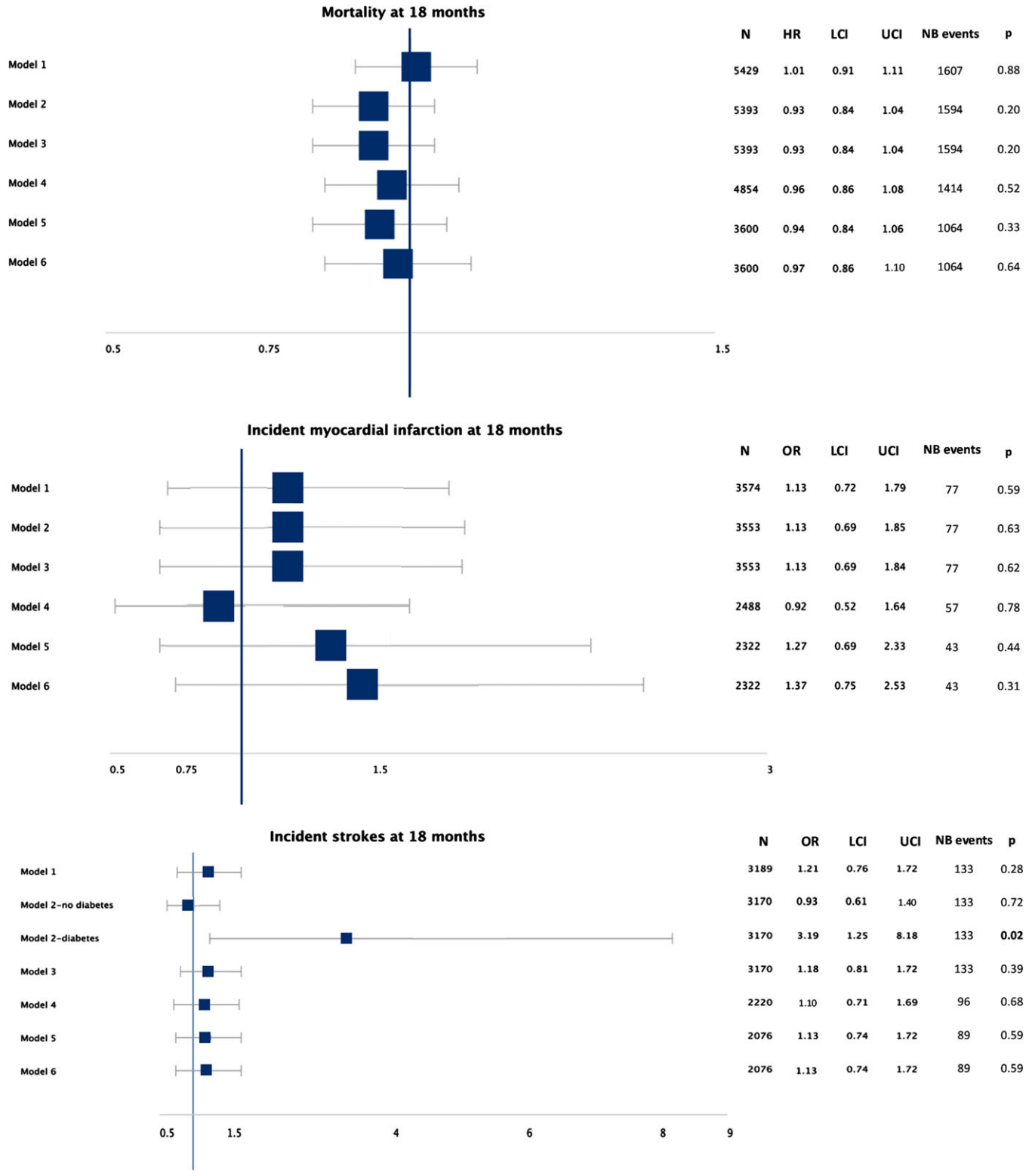

Figure 1. Forest plot of study outcomes. Model 1: whole population, unadjusted. Model 2: whole population, adjusted on covariates independently associated with acetaminophen intake. Model 3: whole population, adjusted on propensity scores. Model 4: whole population, adjusted on propensity scores, excluding decile(s) that were different between the two groups. Model 5: unadjusted propensity-matched cohort. Model 6: propensity-matched cohort, adjusted on covariates associated after matching with acetaminophen intake. HR, hazard ratio; LCI, lower confidence interval; NB events, number of events; No., population; UCI, upper confidence interval.

acetaminophen group; all *P* values were not significant (using a *P* level of .05).

To study the secondary outcomes (MI and stroke) according to acetaminophen prescription, we used logistic regressions with their odds ratios and 95% CIs because we did not have the dates of these two events.

All statistical analyses were performed using SAS 9.4 software (SAS Institute, Inc, Cary, NC).

Table 2. Propensity Scores for Acetaminophen Intake: Comparison for Each Decile Between the Two Groups

	Acetaminophen[a]			
Decile	Yes	No	*P* Value	*P* Value[b]
1	84, 0.176 ± 0.025	456, 0.170 ± 0.029	.0682	.9739
2	115, 0.231 ± 0.014	424, 0.229 ± 0.013	.1839	.9363
3	145, 0.273 ± 0.012	394, 0.273 ± 0.012	.9184	.8383
4	166, 0.313 ± 0.012	373, 0.312 ± 0.012	.4235	.9817
5	184, 0.356 ± 0.013	356, 0.356 ± 0.012	.6405	.9670
6	246, 0.401 ± 0.013	292, 0.402 ± 0.014	.4150	.2919
7	257, 0.454 ± 0.018	283, 0.453 ± 0.017	.3180	.6821
8	294, 0.530 ± 0.024	246, 0.526 ± 0.024	.0939	.1996
9	334, 0.632 ± 0.035	205, 0.627 ± 0.031	.1250	.5414
10	395, 0.768 ± 0.053	144, 0.749 ± 0.043	**<.0001**	.8127

[a]Data are given as number, mean ± SD.
[b]*P* value after propensity score matching.

RESULTS

Our study population for our primary outcome was 5429 subjects (Figure 2); 3190 subjects (58.8%) were not taking acetaminophen, and 2239 subjects (41.2%) were taking acetaminophen.

To study our secondary outcomes, we excluded deceased subjects (n = 1629) and subjects with a history of MI (n = 243) or stroke (n = 628) (Tables S4 and S5).

Population characteristics for our primary outcome are presented in Table 1; mean age was 86.1 ± 8.1 years, and 73.9% were women. Acetaminophen users were older (87.0 ± 7.5 vs 85.4 ± 8.4 years; $P < .0001$). Their GIR group[22] also reflected less autonomy (2.9 ± 1.4 vs 2.7 ± 1.5; $P < .001$). They had more hypertension (56.9% vs 50.5%), more peripheral vascular diseases (19.5% vs 16.9%), and more depression (37.2% vs 32.0%) but less dementia (36.2% vs 46.8%). Pain complaint and evaluation of pain with validated scales were also more frequent in the intake group (37.5% vs 14% and 15.1% vs 7.4%, respectively). Mean intake was 2352 ± 993 mg.

Independent covariates associated with acetaminophen intake at month 0 are shown in Table 3.

Incident mortality was 22.34 per 100 person-years in subjects taking acetaminophen (95% CI = 20.64-24.03 per 100 person-years), with 667 deaths. It was 22.16 per 100 person-years in subjects not taking acetaminophen (95% CI = 20.75-23.58 per 100 person-years), with 940 deaths ($P = .8809$). Supplementary Material S7 provides data for incident mortality per dose subrange, and Table S1 provides data for the effect of acetaminophen intake per dose on mortality.

In our propensity-matched population (n = 3600), incident mortality was 21.56% person-years (95% CI = 19.71%-23.41% person-years), with 520 deaths, in subjects taking acetaminophen; and 22.88% person-years (95% CI = 20.95%-24.80% person-years), with 544 deaths, in subjects not taking acetaminophen ($P = .3283$). In this population, for each dose we had: for 100 to 1000 mg/d, n = 48 deaths, incidence = 23.65% person-years (95% CI = 16.96%-30.34% person-years); for 1000 to 2000 mg/d, n = 118 deaths, incidence = 21.90% person-years (95% CI = 17.95%-25.85% person-years); for 2000 to 3000 mg/d, n = 78 deaths, incidence = 19.00% person-years (95% CI = 14.78%-23.21% person-years); and for 3000 mg/d or more, n = 276 deaths,

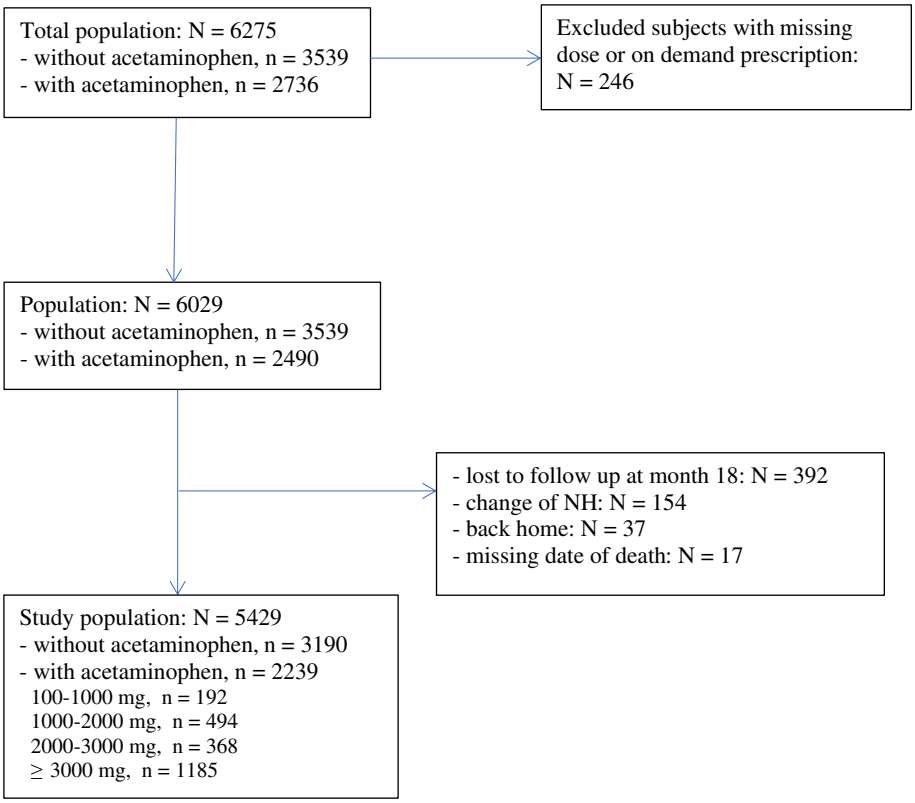

Figure 2. Flowchart of study population. NH, nursing home. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3. Factors Independently Associated With Acetaminophen Use: Logistic Regression Results

	Acetaminophen Use at M0, Yes (n = 2220) vs No (n = 3173)		
Covariates at M0 (N = 5393)	OR	95% CI	*P* Value
Sex (men vs women)	0.75	0.65-0.86	<.0001
Age (y)	1.02	1.01-1.03	<.0001
Length of stay in NH (y)	0.98	0.97-0.99	.0011
Last GIR group	1.08	1.03-1.13	.0015
Diabetes (yes vs no)	0.80	0.68-0.95	.0083
Connective tissue disease (yes vs no)	0.55	0.35-0.89	.0143
Dementia (yes vs no)	0.67	0.59-0.77	<.0001
Psychiatric disease, except depression (yes vs no)	0.84	0.71-0.99	.0384
Fracture(s) (yes vs no)	1.52	1.34-1.73	<.0001
Falls in the previous year (yes vs no)	1.21	1.07-1.37	.0025
Pain with a validated scale (yes vs no)	1.49	1.22-1.81	<.0001
Pain complaint (yes vs no)	2.87	2.49-3.31	<.0001
No. of prescriptions, except acetaminophen			<.0001
≤5	1		
6-10	1.53	1.33-1.75	<.0001
>10	2.34	1.95-2.81	<.0001

Abbreviations: CI, confidence interval; NH, nursing home; OR, odds ratio. GIR groupe iso ressource, refers to autonomy (see supplementary material S7) M0, month 0, beginning of follow-up period.

incidence = 21.91% person-years (95% CI = 19.33%-24.50% person-years). Supplementary Material S7 provides more information on matching.

In all of our models, there was no effect of acetaminophen intake on mortality and no dose-response relationship. Our results are stable as our HR varies between 0.93 and 0.97 (Figure 1) when adjusted to factors associated with acetaminophen intake.

As concerns our secondary outcomes, in our total population (N = 3574), we had 77 MIs (2.15%) between month 0 and month 18, with 34 (2.31%) in subjects taking acetaminophen and 43 (2.04%) in untreated subjects (*P* = .5890). Supplementary Material S7 and Table S2 provide data for incident MI per dose subrange.

In our propensity-matched population (N = 2322), we found 43 MIs (1.85%) between month 0 and month 18, with 24 (2.07%) in subjects taking acetaminophen and 19 (1.64%) in untreated subjects (*P* = .4415).

In this population, for doses of 100 to 1000 mg/d, we found 2 MIs (2.00%); for 1000 to 2000 mg/d, 5 MIs (1.92%); for 2000 to 3000 mg/d, 6 MIs (3.00%); and for 3000 mg/d or more, 11 MIs (1.83%).

Once more, for this outcome, in all models that were run, there was no effect of acetaminophen on MI incidence between month 0 and month 18 and there was no dose-response relationship to be observed.

As for our last outcome, in our total population (N = 3189) we found 133 strokes (4.17%) between month 0 and month 18, with 60 subjects (4.64%) taking acetaminophen and 73 untreated subjects (3.85%) (*P* = .2765). Supplementary Material S7 and Table S3 provide data for incident stroke per dose subrange.

In our propensity-matched population (N = 2076), we found 89 strokes (4.29%) between month 0 and month 18, with 47 subjects (4.53%) treated with acetaminophen and 42 untreated subjects (4.05%) (*P* = .5880).

In this population, for doses of 100 to 1000 mg/d, we found 5 strokes (5.43%); for 1000 to 2000 mg/d, 9 strokes (3.70%); for 2000 to 3000 mg/d, 11 strokes (6.43%); and for 3000 mg/d or more, 22 strokes (4.14%).

We found no effect of acetaminophen or dose-response relationship on the incidence of strokes between month 0 and month 18, except in our M2 model adjusted on factors associated with acetaminophen intake in our total population. In this model, the effect of acetaminophen intake on the incidence of strokes is different between subjects with or without diabetes (acetaminophen × diabetes interaction, *P* = .0167). We observed acetaminophen intake to increase stroke risk in diabetic subjects (HR = 3.19; 95% CI = 1.25-8.18; *P* = .0157), whereas it did not in nondiabetic subjects (HR = 0.93; 95% CI = 0.61-1.40; *P* = .7244).

DISCUSSION

This study provides new observational data about acetaminophen safety in a population having a greater overall risk for adverse effects. We found no increase in death and MI between acetaminophen users and nonusers after an 18-month follow-up in a large sample of NH residents. There was no dose-response relationship to be observed. These results are coherent with current knowledge on the safety of this much-used molecule.[2] As it is the most used analgesic molecule among older adults, whose population is most likely to experience stroke and MI,[23] our results vouch for its continued use at standard doses. We did, however, find an increased risk of strokes in diabetic subjects taking acetaminophen in one of our models.

What Should We Make of This?

Acetaminophen's mechanisms of action are under close scrutiny. It is reported that it acts in a way similar to nonsteroidal anti-inflammatory drugs (NSAIDs) with a twist.[4,24] Cyclooxygenase inhibition (COX 1 and COX 2) results in diminished prostaglandin (PG) synthesis at low rates,[4] bringing about the validation of synergistic use with NSAID in pain management[25] but is not significant enough to suppress platelet function the way NSAID do,[24] probably resulting in fewer gastrointestinal effects. Based on our results, negative COX inhibition effects[26–30] do not seem to weigh on hard outcomes, such as death and MI, in this population.

However, one of our models did find a positive association between acetaminophen use and strokes in diabetic subjects in our population.

Diabetes mellitus affects the vascular system by increasing arteriosclerosis, remodeling vessels with a decrease of lumen, diminishing capillary density, and increasing vessel leakage.[31] Chronic inflammation, endothelial dysfunction, and hypercoagulability result in macrovascular complications, such as strokes.[32]

Moreover, type 2 diabetes, more prominent in older subjects, is responsible for nonalcoholic fatty liver disease, with a prevalence in 70% of patients.[33]

Diminished PG synthesis from acetaminophen intake could result in diminished vasodilation and favored platelet aggregation. Acetaminophen is also known to decrease glutathione levels, resulting in increased inflammation.[34] Adding to that, chronic use may affect an already diminished liver function.

Acetaminophen, in older diabetic patients, could become a triggering factor for strokes.

Finally, the absorption, distribution, detoxification, and elimination properties of any drug are now shown to depend on individual factors, which can have an influence on occurrence of AEs, demonstrated for acetaminophen.[35]

The main limitation of this study is its observational nature. Prescription was collected at baseline, which does not preclude the prescription of acetaminophen during the following months and before inclusion. However, previous studies have reported that prescription in NHs is usually stable; and we presume, from studies performed in the same cohort,[36] that pain, the main complaint justifying prescription, was stable in this population. This observational research is also relevant because the probability that future large randomized controlled trials will investigate acetaminophen safety is low and AEs are known to be poorly reported to the national drug agency when they occur in older people, especially in an NH population. The strength of this research is mainly to have recorded all cardiovascular events and deaths, to have analyzed all the prescriptions of the residents, with few dropouts, and to have a large and poorly investigated frail population with a high risk of AEs. What is more, administration of drugs is mainly under the responsibility of nurses in NHs, and this guarantees dose delivery in this population compared to community-dwelling older people. Finally, the use of propensity-based statistical techniques means our results approach those of a randomized trial in terms of quality and low probable bias.

We cannot exclude that pain management with acetaminophen might induce secondary benefits, such as increased activity, increased food intake, and better psychic health, resulting in decreased adverse effects indirectly. These balance factors were not considered in our models. We could also argue that acetaminophen's adverse effects do not weigh sufficiently against our population's already high morbidity and polypharmacy, despite treatment propensity score matching and adjustments.

As Roberts et al[12] point out, every prescribing decision involves a risk-benefit calculation. Pain can be treated simply, but we must ensure our therapeutic arsenal is safe. Pain management in NHs remains a health priority that is still insufficiently addressed.[15,16] From our current standpoint, acetaminophen still represents a safe first-line choice in pain management for most as there was no association of acetaminophen intake with death and MI. As we have also shown, it could affect our diabetic patients' management. Therapeutic alternatives like morphine exist, but should only be prescribed when needed, as second-line therapy. As our population gets older and frailer, studies need to focus on the safety of the drugs these frail older adults commonly use to better our practice.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Mortality Results in Dose Subrange Groups
Table S2. MI Results in Dose Subrange Groups
Table S3. Stroke Results in Dose Subrange Groups
Table S4. Flowchart MI Study Population
Table S5. Flowchart Stroke Study Population
Figure S6. Kaplan-Meier survival curve for the unadjusted population.
Supplementary Study Material S7: Confounders, covariates independently associated with acetaminophen use, acetaminophen propensity score calculation, matching, incident mortality per dose subrange, incident myocardial infarction per dose subrange, and incident strokes per dose subrange.