ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

Ατμοσφαιρική Ρύπανση, Κλιματική Αλλαγή και Χημική Ρύπανση: Παράγοντες Κινδύνου για Καρδιαγγειακή Νόσο στις Χώρες Μέτριου και Χαμηλού Εισοδήματος- Συστηματική Ανασκόπηση

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Air Pollution, Climate Change and Chemical Pollution: Risk Factors of Cardiovascular Disease in LMICs- A Systematic Review

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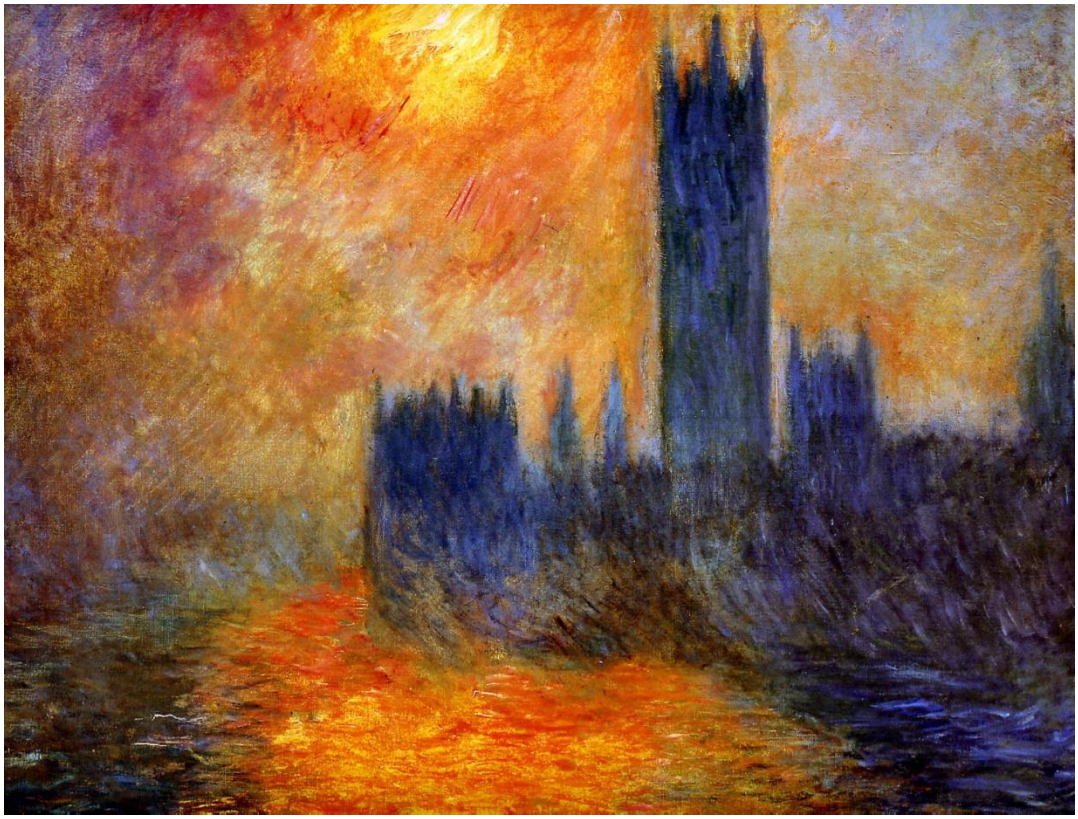

Claude Monet (1840-1926) London, Houses of Parliament. The Sun Shining through the Fog 1904.

Abbreviations

AAP	Ambient Air Pollution
CVD	Cardiovascular Disease
ER	Emergency Room
HICs	High Income Countries
IHD	Ischemic Heart Disease
LMICs	Low and Middle Income Countries
NCDs	Non Communicable Diseases
PM	Particulate Matter
CO2	Carbon Dioxide
CO	Carbon Monoxide
WHO	World Health Organization

Περίληψη στα Ελληνικά

«Ατμοσφαιρική Ρύπανση, Κλιματική Αλλαγή και Χημική Ρύπανση: Παράγοντες Κινδύνου για Καρδιαγγειακή Νόσο στις Χώρες Μέτριου και Χαμηλού Εισοδήματος- Συστηματική Ανασκόπηση»

Λέξεις κλειδιά: Ατμοσφαιρική Ρύπανση, Κλιματική Αλλαγή, Χημική Ρύπανση, Καρδιαγγειακή Νόσος, Χώρες Μέτριου και Χαμηλού Εισοδήματος

Γενική Εισαγωγή

Η καρδιαγγειακή νόσος είναι η κυρίαρχη αιτία νοσηρότητας και θνησιμότητας παγκοσμίως. Η Ισχαιμική Καρδιακή Νόσος (ΙΚΝ) και το Αγγειακό Εγκεφαλικό Επεισόδιο (ΑΕΕ) ευθύνονται για τα δύο τρίτα των θανάτων παγκοσμίως και η πλειονότητα αυτών των θανάτων συμβαίνει σε χώρες μετρίου και χαμηλού εισοδήματος (LMICs). Η επίπτωση της καρδιαγγειακής νόσου στις LMICs αυξάνεται ραγδαία τις τελευταίες δεκαετίες και η αύξηση αυτή δεν μπορεί να αποδοθεί αποκλειστικά στους παραδοσιακούς, συμπεριφορικούς παράγοντες κινδύνου, όπως είναι το κάπνισμα, η διατροφή κτλ. Το γεγονός αυτό υποδηλώνει ότι ενδεχομένως να υπάρχουν επιπρόσθετοι παράγοντες κινδύνου, οι οποίοι δεν έχουν μελετηθεί εις βάθος και οι οποίοι αυξάνουν την επίπτωση της νόσου στις LMICs. Η ατμοσφαιρική ρύπανση, η κλιματική αλλαγή και η χημική μόλυνση επηρεάζουν δυσανάλογα τις LMICs σε σχέση με τις χώρες υψηλού εισοδήματος (HICs), συνεπώς θα μπορούσαν να τελούν σημαντικό ρόλο στην επίπτωση της νόσου. Σκοπός της εργασίας είναι, μέσω συστηματικής ανασκόπησης της βιβλιογραφίας, να αποσαφηνιστεί η ύπαρξη μιας τέτοιας σχέσης, αυτή η σχέση να ποσοτικοποιηθεί και τελικώς, να προταθούν στόχοι και πεδία για μελλοντική έρευνα στο συγκεκριμένο πεδίο.

Μεθοδολογία

Πραγματοποιήθηκε μια συστηματική ανασκόπηση της βιβλιογραφίας, με βάση τη μέθοδο PRISMA, σε τρία στάδια. Πιο συγκεκριμένα, πραγματοποιήθηκε συλλογή δεδομένων από το PubMed, ScienceDirect, αλλά και από γκρίζα βιβλιογραφία, όπως αναφορές του

Παγκόσμιου Οργανισμού Υγείας κτλ., ακολούθησε διαλογή με βάση τον τίτλο και την περίληψη και τέλος ανάγνωση του πλήρους κειμένου και εξαγωγή δεδομένων. Χρησιμοποιήθηκαν άρθρα, τα οποία εκδόθηκαν από το Γενάρη του 2010 ως το Γενάρη του 2020, με σκοπό να αναδείξουμε τη σχέση της καρδιαγγειακής νόσου με την ατμοσφαιρική ρύπανση, την κλιματική αλλαγή και την μόλυνση από χρήση χημικών ουσιών, στις LMICs. Πιο συγκεκριμένα, τα κλινικά αποτελέσματα που διερευνήσαμε ήταν η νοσηρότητα και η θνησιμότητα από ΑΕΕ και ΙΚΝ, με απώτερο σκοπό να απαντηθούν συγκεκριμένα ερευνητικά ερωτήματα και πιο συγκεκριμένα, ποια είναι η σχέση της συγκέντρωσης των περιβαλλοντικών ρύπων, με τη νοσηρότητα και τη θνησιμότητα από καρδιαγγειακή νόσο, ποια είναι η σχέση της θερμοκρασίας με τη νοσηρότητα και τη θνησιμότητα από καρδιαγγειακή νόσο και ποια είναι η σχέση των χημικών ρύπων με τη νοσηρότητα και τη θνησιμότητα από καρδιαγγειακή νόσο.

Η αναζήτηση της βιβλιογραφίας έγινε με βάση «λέξεις-κλειδιά», στις βάσεις δεδομένων και στη συνέχεια, οι τίτλοι και οι περιλήψεις ελέγχθηκαν αρχικά, για συνάφεια με το ερευνητικό ζήτημα. Σε επόμενο στάδιο, έγινε ανάγνωση του πλήρους κειμένου από τα επιλεγμένα άρθρα. Στην τελική επεξεργασία των δεδομένων, συμπεριλήφθηκαν μόνο έρευνες από LMICs, με βάση τον ορισμό της Παγκόσμιας Τράπεζας. Επίσης, συμπεριλήφθηκαν μόνο άρθρα που παρέθεταν δείκτες θνησιμότητας, αριθμό επισκέψεων σε τμήμα επειγόντων περιστατικών και αριθμό νοσηλειών και τα οποία συνόδευαν τα αποτελέσματά τους με διαστήματα αξιοπιστίας. Αποκλείστηκαν άρθρα, τα οποία δεν περιέγραφαν λεπτομερώς τη μεθοδολογία, τα χαρακτηριστικά του υπό μελέτη πληθυσμού, καθώς και αυτά που αφορούσαν ατμοσφαιρική ρύπανση εσωτερικού χώρου, κλασικούς παράγοντες καρδιαγγειακής νόσου ή βιοδείκτες. Επίσης, αποκλείστηκαν άρθρα με αυτό-αναφερόμενη θνησιμότητα, καθώς και μεμονωμένες αναφορές περιστατικών (case studies). Συνολικά, συλλέχθηκαν 3991 άρθρα, ενώ στο τελικό κείμενο συμπεριλαμβάνονται 107 και στην ανάλυση δεδομένων, 31 άρθρα.

Επιδημιολογία της Καρδιαγγειακής Νόσου

Τα τελευταία 20 χρόνια, ο συνολικός αριθμός των θανάτων από καρδιαγγειακή νόσο αυξήθηκε κατακόρυφα, σε 17.3 εκατομμύρια θανάτους το χρόνο. Μέχρι πρόσφατα, θεωρούνταν ασθένεια του ανεπτυγμένου κόσμου, καθώς και ασθένεια που έπληττε αποκλειστικά τους ηλικιωμένους. Ωστόσο, τα τελευταία χρόνια, στις LMICs, παρατηρείται

το φαινόμενο της επιδημιολογικής μετάβασης και οι χώρες αυτές εμφανίζουν σταδιακά, επιδημιολογικά πρότυπα που απαντώνται στις χώρες υψηλού εισοδήματος (HICs). Ταυτόχρονα, η επίπτωση της νόσου τείνει να αυξάνεται στις νεαρές ηλικίες.

Οι χώρες της Νοτιοανατολικής Ασίας, η υποσαχάριος Αφρική και τα νησιά της Καραϊβικής, είναι ανάμεσα στις χώρες που μαστίζονται περισσότερο από τα Μη Μεταδοτικά Νοσήματα (NCDs). Από τους συνολικά 25.3 εκατομμύρια συνολικούς θανάτους στις παραπάνω χώρες, τα 14 εκατομμύρια αποδίδονται σε NCDs και συμβαίνουν σε μικρότερες ηλικίες σε σχέση με τις HICs. Γενικώς, οι LMICs πλήττονται σε δυσανάλογο βαθμό από την καρδιαγγειακή νόσο, σε σχέση με τις HICs. Πιο συγκεκριμένα, από το 1990 ως το 2013 σημειώθηκε αύξηση του επιπολασμού της νόσου κατά 83% στην υποσαχάριο Αφρική και 97% στην Νότια Ασία. Η Ινδία επίσης, είναι η χώρα με την μεγαλύτερη απώλεια σε παραγωγικά έτη ζωής και υπολογίζεται πως αυτή η απώλεια θα είναι 940% υψηλότερη σε σχέση με τις Ηνωμένες Πολιτείες της Αμερικής.

Η Επιδημιολογική Μετάβαση στις LMICs

Η κατακλυσμιαία αύξηση της επίπτωσης των NCDs και συγκεκριμένα, της καρδιαγγειακής νόσου στις LMICs, είναι απότοκος γεωγραφικών, ιστορικών και κοινωνικών αλλαγών, οι οποίες διαμόρφωσαν με την πάροδο των χρόνων ένα επιδημιολογικό μοντέλο που χαρακτηρίζεται από χαμηλό αριθμό γεννήσεων, αύξηση του προσδόκιμου επιβίωσης και συνεπώς, γήρανση του πληθυσμού καθώς και επικράτηση των NCDs ως κύρια αιτία νοσηρότητας και θνητότητας. Πρόκειται για το στάδιο των «manmade diseases", σύμφωνα με το μοντέλο του Όμραν. Ενδεικτική είναι η κατάσταση στην Ανατολική Μεσόγειο, όπου το προσδόκιμο επιβίωσης αυξήθηκε από τα 65 έτη στα 71 έτη, σε μόλις 13 χρόνια, την ίδια στιγμή ο επιπολασμός της καρδιαγγειακής νόσου αυξήθηκε κατά 17%.

Η επιταχυνόμενη αστικοποίηση που παρατηρείται στην Αφρική και στην Ασία, στα πλαίσια της απότομης οικονομικής ανάπτυξης αυτών των περιοχών. Ταυτόχρονα σχετίζεται με την επισιτιστική ανασφάλεια, την αυξημένη ξηρασία λόγω της κλιματικής αλλαγής, αλλά και τις βίαιες δημογραφικές αλλαγές, μέσω της μετανάστευσης, της γεωπολιτικής αστάθειας και των κοινωνικών ανισοτήτων που οξύνονται διαρκώς. Το 2014, το 54% του παγκόσμιου πληθυσμού κατοικούσε σε αστικά κέντρα και το ποσοστό αυτό προβλέπεται να φτάσει το 66% μέχρι το 2050, ενώ στη Λατινική Αμερική το ποσοστό αυτό

είναι ήδη 90%. Η αστικοποίηση αποτελεί δυναμική κοινωνική διαδικασία, αφού διαμορφώνει το περιβάλλον μέσα στο οποίο οι άνθρωποι ζουν και εργάζονται. Ταυτόχρονα, προωθεί την υιοθέτηση ενός τρόπου ζωής, ο οποίος αποτρέπει τη σωματική άσκηση και προάγει την κακή διατροφή, το στρες, και την απομόνωση. Συνολικά δηλαδή, ευνοεί την εμφάνιση παραγόντων που ευνοούν την εμφάνιση καρδιαγγειακής νόσου. Επιπροσθέτως, η αστικοποίηση και η εκβιομηχάνιση συνδέονται άρρηκτα με την ατμοσφαιρική ρύπανση και την κλιματική αλλαγή, παράγοντες που πιθανώς να αυξάνουν την επίπτωση της καρδιαγγειακής νόσου στις LMICs. Τέλος, υποστηρίζεται η υπόθεση πως η αστικοποίηση δύναται να επηρεάσει ακόμη και την γονιδιακή έκφραση πρωτεϊνών που σχετίζονται με την υπέρταση και άλλους σχετικούς παράγοντες κινδύνου.

Ατμοσφαιρική Ρύπανση και Καρδιαγγειακή Νόσος

Η ατμοσφαιρική ρύπανση αποτελεί σημαντική απειλή για τον παγκόσμιο πληθυσμό και ταυτόχρονα ένα μείζον θέμα Δημόσιας Υγείας. Ευθύνεται για παραπάνω από 7 εκατομμύρια ετήσιους θανάτους, οι οποίοι σχετίζονται κυρίως με τα NCDs και συγκεκριμένα, με την καρδιαγγειακή νόσο. Η ατμοσφαιρική ρύπανση είναι επακόλουθο της ανεξέλεγκτης αστικοποίησης και εκβιομηχάνισης. Το 80% των αστικών κέντρων υπερβαίνουν τα όρια του που θεσπίζει ο ΠΟΥ ως ανώτερο επιτρεπόμενο επίπεδο ρύπανσης. Οι περισσότερες από αυτές περιοχές ανήκουν στις LMICs.

Ανάμεσα στις πλέον πληττόμενες από τη ρύπανση χώρες, βρίσκεται η Κίνα, μια ταχέως εξελισσόμενη παγκόσμια οικονομία, που βασίζεται στη βαριά βιομηχανία και διοχετεύει στο περιβάλλον πάνω από 5000 δισεκατομμύρια κιλά διοξειδίου του άνθρακα ετησίως. Ταυτόχρονα, η Ινδία, το Πακιστάν, οι χώρες της Νοτιοανατολικής Ασίας και του Δυτικού Ειρηνικού, είναι ανάμεσα στις περιοχές με τις υψηλότερες συγκεντρώσεις ατμοσφαιρικών ρύπων στον κόσμο. Στην πραγματικότητα, σε αυτές τις χώρες, απαντάται το 91% των συνολικών θανάτων που οφείλονται στην ατμοσφαιρική ρύπανση. Παρόλο που η επίπτωση της καρδιαγγειακής νόσου και τα επίπεδα ρύπανσης στις LMICs αυξάνονται ραγδαίως, η έρευνα σε αυτό το πεδίο είναι περιορισμένη σε αυτές τις χώρες. Παράγοντες που δυσχεραίνουν περαιτέρω την κατάσταση είναι η ανεπαρκής περιβαλλοντική νομοθεσία, και η δυσπραγία των συστημάτων υγείας.

Οι πιο κοινές πηγές των ατμοσφαιρικών ρύπων είναι οι εκπομπές των αυτοκινήτων (25%) και της βιομηχανίας (15%), κυρίως ο τομέας της παραγωγής ηλεκτρικής ενέργειας. Επίσης, σε μεγάλο βαθμό οι ρύποι προέρχονται από τη γεωργία και την καύση των απορριμμάτων (16). Οι πλέον επιβλαβείς ουσίες για τον άνθρωπο είναι το Διοξείδιο του Άνθρακα, το Όζον, ο Άνθρακας και τα Αιωρούμενα Σωματίδια (Α.Σ.) Τα τελευταία, είναι οι ουσίες που έχουν μελετηθεί περισσότερο, καθώς θεωρούνται οι πιο επιβλαβείς για την υγεία.

Ανάλογα με τη διάμετρο τους, τα Α.Σ. εμφανίζουν διαφορετική παθοφυσιολογική συμπεριφορά μέσα στον ανθρώπινο οργανισμό. Όσο μικρότερο είναι το μέγεθός τους, τόσο πιο έντονη διεισδυτική ικανότητα διαθέτουν. Συγκεκριμένα, Α.Σ. που είναι παράγωγα της βενζίνης και του ντίζελ, είναι ιδιαιτέρως διεισδυτικά, εισέρχονται στην κυκλοφορία του αίματος και σχετίζονται με την εμφάνιση ΑΕΕ και ΙΚΝ. Ο ακριβής μηχανισμός δεν είναι απόλυτα ξεκάθαρος. Ωστόσο, η επικρατούσα θεωρεία υποστηρίζει πως η μακροχρόνια έκθεση σε αυξημένες συγκεντρώσεις Α.Σ., προάγει τη χρόνια φλεγμονή και το οξειδωτικό στρες. Ταυτόχρονα, τα Α.Σ. προάγουν την αθηρογένεση και τις διαταραχές τους αυτόνομου νευρικού συστήματος, οδηγώντας σε αγγειακή ισχαιμική νόσο και αρρυθμίες, αντίστοιχα.

Η σχέση των ατμοσφαιρικών ρύπων με την θνητότητα της καρδιαγγειακής νόσου, έχει μελετηθεί στις LMICs, σε περιορισμένο βαθμό. Οι περισσότερες μελέτες έχουν πραγματοποιηθεί στην Κίνα, λιγότερες στην Λατινική Αμερική και σε χώρες της Νοτιοανατολικής Ασίας. Πρόκειται κυρίως για διαχρονικές μελέτες, οι οποίες δηλαδή σκοπό έχουν να παρατηρήσουν την επίδραση ενός φαινομένου σε ένα δείγμα. Στην προκειμένη, σκοπό έχουν να συσχετίσουν την αυξημένη συγκέντρωση των ρύπων, με την αύξηση στην καρδιαγγειακή θνησιμότητα (Σχετικός Κίνδυνος- Σ.Κ.). Μια έρευνα στο Πεκίνο, μια πόλη με μέσα επίπεδα Α.Σ. 96.2μg/m^3, αύξηση της συγκέντρωσης των Α.Σ. κατά 10μg/m^3, βρέθηκε να προκαλεί αύξηση 0.25% (95% CI: 0.16, 0.34) στην καρδιαγγειακή θνησιμότητα. Αντίστοιχα, στην πόλη Λαντζού για αύξηση 10μg/m^3,παρατηρήθηκε αύξηση στην θνησιμότητα από ΑΕΕ, κατά 1.22% (95% CI: 0.11, 2.35) την τέταρτη ημέρα μετά την έκθεση του πληθυσμού σε υψηλά επίπεδα ρύπανσης.

Η Κίνα αντιπροσωπεύει ένα μεγάλο ποσοστό μελετών πάνω στη σχέση της καρδιαγγειακής νόσου με την ατμοσφαιρική ρύπανση, καθώς πλήττεται σοβαρά από αυτή. Η CAPES, μια μεγάλη μελέτη στην Κίνα, που περιλάμβανε 16 πόλεις με 96 εκατομμύρια κατοίκους, βρήκε πως μια αύξηση των Α.Σ. κατά 10μg/m^3, σχετίζεται με αύξηση της

θνησιμότητας κατά 0.43% (95%CI:0.37,0.49%). Πιο αυξημένος αντίστοιχος Σ.Κ. παρατηρήθηκε στο Μεξικό, χωρίς όμως στατιστικά σημαντικά αποτελέσματα, με αύξηση στη θνητότητα του ΑΕΕ κατά 3.43% (95%CI: 0.10, 6.28) και αύξηση στην ΙΚΝ κατά 1.22% (95%CI: 0.17, 2.28) (23). Σε μια από τις πολυκεντρικές μελέτες της Λατινικής Αμερικής, η ο κίνδυνος ήταν 0.72% (95%CI: 0.54, 0.89). Είναι εμφανές ότι τα αποτελέσματα από τις διάφορες μελέτες δε διαφέρουν σημαντικά, ωστόσο, λίγες είναι αυτές που παραθέτουν στατιστικά σημαντικά αποτελέσματα. Σε μια άλλη έρευνα στην Κίνα, η οποία συμπεριέλαβε 70.947 άτομα, ελέγχθηκε η σχέση της μακροχρόνιας έκθεσης σε διάφορους ρύπους, με την καρδιαγγειακή θνησιμότητα, σε ένα διάστημα 9 χρόνων. Αύξηση 10μg/m^3 σε Α.Σ., Διοξείδιο του Θείου και Μονοξείδιο του Αζώτου, βρέθηκε να αντιστοιχεί σε αύξηση της θνητότητας κατά 0.9% (95% CI: 0.3, 1.5), 3.2 (95% CI: 2.3, 4.0) και 2.3 (95% CI: 0.6, 4.1), αντίστοιχα. Στην Ναγγίν της Κίνας το 2016, το ΑΕΕ αποτελούσε το 44% των θανάτων από ατμοσφαιρική ρύπανση και η ΙΚΝ το 28%, ενώ στο Βαράνασι της Ινδίας από το 2003 ως το 2015, τα αντίστοιχα ποσοστά ήταν 18% και 29%.

Σχετικά με την καρδιαγγειακή νοσηρότητα, μια έρευνα στο Πακιστάν, ανέδειξε Σ.Κ.=1.14 (95% CI:1.04,1.25) για τις αυξημένες ατμοσφαιρικές τιμές Νικελίου και 1.21 (95%CI:1.03,1.43) για το Αλουμίνιο, ενώ στο Πεκίνο αύξηση στη συγκέντρωση των Α.Σ. κατά 10 μg/m^3, σχετίστηκε με αύξηση του Σ.Κ. για νοσηλεία από ΙΚΝ, κατά 0.56% (95%CI: 0.16, 0.95). Αντιθέτως, σε μια μεγαλύτερη μελέτη στην Κίνα, αντίστοιχη αύξηση στη συγκέντρωση των Α.Σ. σχετίστηκε με αύξηση των περιπτώσεων ΑΕΕ κατά 1.16 (95%CI: 1.03, 1.30). Παρόμοια αποτελέσματα ανέδειξε μία από τις ελάχιστες πολυκεντρικές μελέτες κοορτής σε LMICs, που περιλάμβανε τη Γκάνα, την Ινδία, το Μεξικό και τη Νότια Αφρική. Εκεί, ο συνολικός λόγος σχετικών πιθανοτήτων για την εμφάνιση ΑΕΕ, στις περιπτώσεις υψηλής ατμοσφαιρικής ρύπανσης, ήταν 1.13 (95% CI: 1.04, 1.22).

Για αύξηση στη συγκέντρωση των Α.Σ. κατά 10μg/m^3, η αύξηση στην καρδιαγγειακή θνησιμότητα και νοσηρότητα κυμαινόταν από 0.25% ως 1.22% και από 0.14% ως 0.26% αντίστοιχα. Η αντίστοιχη αύξηση στη θνησιμότητα και στη νοσηρότητα από ΑΕΕ κυμαινόταν από 1.22% ως 3.43% και από 1.16% ως 1.37% αντίστοιχα. Τα αποτελέσματα των μελετών που συμπεριλήφθηκαν δεν παρουσιάζουν μεγάλες αποκλίσεις, ωστόσο η γενίκευσή τους δεν είναι ασφαλής. Ένας από τους κύριους λόγους είναι ότι έχουν χρησιμοποιηθεί διαφορετικές μεθοδολογίες, οι πληθυσμοί παρουσιάζουν ετερογένειες και οι μετρήσεις των ρύπων έχουν γίνει με διαφορετικούς τρόπους. Επίσης, δεν αξιολογήθηκαν οι ίδιοι συγχυτικοί παράγοντες, όπως οι μετερεωλογικές συνθήκες, αν και είναι γνωστό ότι

αυτές επηρεάζουν σε κάποιο βαθμό την επίδραση της έκθεσης. Στις περιπτώσεις που βρέθηκαν παρόμοια αποτελέσματα, αυτά αφορούσαν συχνά σε διαφορετικές ημέρες μετά την αρχική έκθεση (Lag Days). Επιπροσθέτως, στις μελέτες της θνησιμότητας, δεν ήταν ξεκάθαρο αν η το διάστημα αφορούσε την ημέρα εμφάνισης των συμπτωμάτων ή την ημέρα θανάτου. Είναι βασικό να τονίσουμε πως στις περιβαλλοντικές μελέτες, είναι χρήσιμο να ελέγχεται το ενδεχόμενο της διαφορετικής έκθεσης των υποπληθυσμών στο ίδιο περιβαλλοντικό φαινόμενο, καθώς και το γεγονός αυτοί μπορούν οι υποπληθυσμοί δύνανται να έχουν διαφορετική ανταπόκριση στα περιβαλλοντικά ερεθίσματα. Ταυτόχρονα, κοινωνικοί προσδιοριστές, οι οποίοι φαίνεται να επηρεάζουν την έκθεση, αλλά και η συνύπαρξη ήδη υπάρχουσας καρδιαγγειακής νόσου, θα πρέπει να λαμβάνονται υπόψιν ως πιθανοί συγχυτικοί παράγοντες, που δύνανται να επηρεάσουν την τελική σχέση.

Κλιματική Αλλαγή

Τα τελευταία 130 χρόνια, η μέση θερμοκρασία της Γης έχει αυξηθεί κατά 0.85°C, με κάθε μια από τις τελευταίες δεκαετίες να είναι πιο ζεστή από όλες τις δεκαετίες μετά το 1850. Ταυτόχρονα, ο ρυθμός της αύξησης της θερμοκρασίας έχει διπλασιαστεί τα τελευταία 50 χρόνια. Η κλιματική αλλαγή είναι άρρηκτα συνδεδεμένη με την ανθρώπινη δραστηριότητα, κυρίως με την μαζική καύση ορυκτών καυσίμων, την αποψίλωση των δασών και τους ταχύτατους ρυθμούς γεωργικής παραγωγής. Όλες οι προαναφερθείσες διαδικασίας, εκλύουν τεράστιες ποσότητες Διοξειδίου του Άνθρακα στην ατμόσφαιρα, οι οποίες παγιδεύονται λόγω των υψηλών θερμοκρασιών επιτείνοντας το «Φαινόμενο του Θερμοκηπίου». Δηλαδή, δημιουργείται ένας φαύλος κύκλος ανάμεσα στην αυξημένη θερμοκρασία και στην ατμοσφαιρική ρύπανση.

Υπολογίζεται πως ανάμεσα στο 2030 και στο 2050, η κλιματική αλλαγή θα ευθύνεται για 250.000 παραπάνω θανάτους το χρόνο και θα προκαλεί ετήσια οικονομική ζημία στα συστήματα υγείας, υπολογιζόμενη από 2 ως 4 δις δολάρια. Μέχρι προσφάτως, θεωρούνταν πως η κλιματική αλλαγή στις LMICs σχετίζεται κυρίως με τις μεταδοτικές ασθένειες και την επισιτιστική ανασφάλεια, με αποτέλεσμα, η σχέση της με την καρδιαγγειακή νόσο, να έχει μελετηθεί μόνο ακροθιγώς. Επίσης, πρέπει να υπογραμμιστεί η ανισότητα που υπάρχει ανάμεσα στις LMICs και στις HICs, καθώς οι πρώτες συνεισφέρουν ελάχιστα στην κλιματική αλλαγή, αλλά πλήττονται δυσανάλογα από τις συνέπειές της. Ταυτόχρονα, αυτές οι χώρες εμφανίζουν την μεγαλύτερη επίπτωση

καρδιαγγειακής νόσου παγκοσμίως, ενώ διαθέτουν συστήματα υγείας που δε δύνανται να ανταπεξέλθουν στις πολλαπλές υγειονομικές προκλήσεις. Χαρακτηριστικό είναι το παράδειγμα των Νήσων του Ειρηνικού, οι οποίες ευθύνονται μόνο για την παραγωγή του 0.03% των συνολικών αερίων του θερμοκηπίου, ωστόσο μαστίζονται από διαρκώς ακραίες θερμοκρασίες, που αποτελούν τροχοπέδη στην ανάπτυξη της περιοχής.

Η επίδραση των ακραίων θερμοκρασιών στο καρδιαγγειακό σύστημα είναι πολυπαραγοντική. Αρχικά, το κρύο προκαλεί αύξηση των κατεχολαμινών, ταχυκαρδία και αύξηση της αρτηριακής πίεσης, ενώ αποτελεί παράγοντα κινδύνου και για αθηρωμάτωση. Από την άλλη, η ζέστη προάγει την αφυδάτωση και την αντιδραστική ταχυκαρδία, ενώ αυξάνει την πηκτικότητα του αίματος. Φαίνεται μάλιστα πως το φαινόμενο του καύσωνα έχει δυο αντίκτυπα στην υγεία, ένα άμεσο, το οποίο εξαρτάται από το ύψος της θερμοκρασίας και ένα δευτερεύον, ανάλογα με τη διάρκεια του φαινομένου. Ενδιαφέρον παρουσιάζει το γεγονός ότι εκτός από την ίδια τη θερμοκρασία, κι άλλοι παράγοντες επιδρούν στη σχέση αυτής με την Καρδιαγγειακή νοσηρότητα και θνησιμότητα. Φαίνεται πως οι πληθυσμοί που ζουν σε συγκεκριμένες περιβαλλοντικές συνθήκες και θερμοκρασίες, σταδιακά προσαρμόζονται στο τοπικό κλίμα. Συγκρινόμενοι με άλλους πληθυσμούς, όταν εκτίθενται σε ένα περιβαλλοντικό ερέθισμα, αντιδρούν διαφορετικά, έχοντας αναπτύξει ένα είδος αντοχής στο συγκεκριμένο ερέθισμα. Έτσι, έχει φανεί ότι πληθυσμοί που είναι λιγότερο πιθανό να εκτίθενται συχνά σε ακραία υψηλές θερμοκρασίες, είναι πιο ευάλωτοι σε αυτές και εμφανίζουν υψηλότερους δείκτες θνητότητας στην περίπτωση ενός καύσωνα. Το αντίστοιχο ισχύει για την έκθεση σε ακραία χαμηλές θερμοκρασίες. Σε μια μελέτη 27 πόλεων στη Βραζιλία, οι χαμηλές και οι υψηλές θερμοκρασίες σχετίστηκαν με αύξηση του Σ.Κ. για καρδιαγγειακή θνησιμότητα κατά 26% (95% CI: 17, 35) και 7% (95%CI:1, 13) αντίστοιχα. Στις πόλεις με ζεστό κλίμα, η θερμοκρασία πέραν της οποίας αυξανόταν σημαντικά η θνητότητα, ήταν υψηλότερη σε σχέση με τις πόλεις με πιο κρύο κλίμα.

Η Αφρική συνεισφέρει ελάχιστα στην κλιματική αλλαγή, ωστόσο πλήττεται από τις συνέπειές της, ενώ είναι ταυτόχρονα η πιο ευάλωτη ήπειρος, λόγω των υψηλών θερμοκρασιών και της χαμηλής της προσαρμοστικής ικανότητας. Η έρευνα στην Αφρική είναι πολύ περιορισμένη, με αντιφατικά αποτελέσματα. Από την άλλη πλευρά, η Κίνα είναι επίσης μια ιδιαιτέρως πληττόμενη από την κλιματική αλλαγή χώρα. Η θερμοκρασία της προβλέπεται να έχει αυξηθεί κατά 6.1°C από το 1900 ως το 2100. Σε μια έρευνα στο Θιβέτ, τις ζεστές μέρες η καρδιαγγειακή θνητότητα αυξήθηκε κατά 2.3 (CI 95%: 1.03, 5.24). Οι

ηλικιωμένοι ήταν πιο ευάλωτοι στις υψηλές θερμοκρασίες. Στο Βιετνάμ, οι ακραία υψηλές θερμοκρασίες σχετίστηκαν με αύξηση στη νοσηρότητα κατά 0.8% (95%CI: -8.2, 3.6), στην επαρχιακή Κίνα με αύξηση 1.28 (95%CI: 1.11, 1.48) (41) και στη Σαγκάη με 8% (95% CI: 5, 11).

Παρότι τα αποτελέσματα από τις μελέτες που συλλέξαμε δε διαφέρουν σημαντικά μεταξύ τους, δεν είναι ασφαλές να γίνουν γενικεύσεις, λόγω της απουσίας κοινών ορισμών για τις υψηλές και χαμηλές θερμοκρασίες. Επίσης, σε πολλές έρευνες δεν έχουν ληφθεί υπόψιν οι ίδιοι συγχυτικοί παράγοντες, όπως η ώρα της ημέρας, το διάστημα μεταξύ των ακραίων φαινομένων, τα επίπεδα της ατμοσφαιρικής ρύπανσης, η πιθανή αστεγία, το φύλο, η κατάσταση της υγείας, η ημέρα της εβδομάδας κτλ. Όλοι αυτοί οι παράγοντες επηρεάζουν την έκθεση του πληθυσμού στη θερμοκρασία του περιβάλλοντος. Ωστόσο, παρατηρήθηκαν κοινά μοτίβα, τα οποία αξίζει να ληφθούν υπόψιν στο μελλοντικό σχεδιασμό μελετών. Αρχικά, στην πλειονότητα των μελετών, η καμπύλη θερμοκρασίας- θνητότητας έχει σχήμα U, υποδηλώνοντας ότι η θνητότητα είναι ελάχιστη στις μέτριες θερμοκρασίες και αυξάνεται στις ακραίες. Το φάσμα αυτών των μέτριων, ήπιων θερμοκρασιών διαφέρει σε διαφορετικές περιοχές, ενισχύοντας την υπόθεση για το σημαντικό ρόλο του τοπικού κλίματος, του γεωγραφικού πλάτους και της προσαρμοστικότητας των πληθυσμών. Επίσης, κοινή παρατήρηση αποτέλεσε το γεγονός ότι η θνητότητα αυξανόταν απότομα στις ηπιότερες μεταβολές της θερμοκρασίας και σταθεροποιούταν στις ακραία υψηλές ή χαμηλές, φαινόμενο το οποίο μπορεί να αποδοθεί στην «μετακινούμενη θνησιμότητα/ mortality displacement».

Χημική Ρύπανση και Καρδιαγγειακή Νόσος

Νεφροπάθεια της Κεντρικής Αμερικής

Εν συνεχεία, θα σχολιασθεί ένα αναδυόμενο ζήτημα Δημόσιας Υγείας στις LMICs. Συγκεκριμένα, πρόκειται μια νόσο των νεφρών, η οποία σχετίζεται με διαταραχές στην αγγειακή κυκλοφορία, όπως ισχύει και στην περίπτωση του ΑΕΕ και της ΙΚΝ. Η νόσος είναι γνωστή ως «Νεφροπάθεια της Κεντρικής Αμερικής»(Mesoamerican Nephropathy-MEN) ή «Νεφρική Νόσος Αγνώστου Αιτιολογίας», λόγω του γεγονότος ότι συνοδεύεται από αυξημένη τιμή κρεατινίνης και πρωτεϊνουρία, εν απουσία προφανών αιτιών νεφρικής ανεπάρκειας, όπως ο Σακχαρώδης Διαβήτης ή η Υπέρταση. Η νόσος καταλήγει σε βαριά

νεφρική ανεπάρκεια, η οποία είναι και η βασική αιτία θανάτου. Ενδημεί σε χώρες της Κεντρικής Αμερικής, κυρίως στην Νικαράγουα και στο Ελ Σαλβαδόρ, όπου μάλιστα αποτελεί την πιο συχνή αιτία πρόωρου θανάτου στους νεαρούς ενήλικες. Το Ελ Σαλβαδόρ μάλιστα, έχει τον υψηλότερο δείκτη θνησιμότητας από χρόνια νεφρική ανεπάρκεια, παγκοσμίως. Η ΜΕΝ επηρεάζει δυσανάλογα τις πιο φτωχές χώρες και αφορά κυρίως, νεαρούς ενήλικους άνδρες, κατοίκους αγροτικών και επαρχιακών περιοχών, που εκτίθενται σε υψηλές θερμοκρασίες και υγρασία. Ο επιπολασμός της νόσου είναι πολύ ψηλός στους εργάτες των ζαχαρότευτλων, οι οποίοι καλούνται να εργαστούν καθημερινά και αδιάκοπα, σε θερμοκρασίες ως και 42°C. Επίσης, αφορά πληθυσμούς που ασχολούνται με την αλιεία και την εξόρυξη ορυκτών.

Η αιτιολογία της νόσου δεν είναι απολύτως ξεκάθαρη. Ωστόσο, πολλοί επιστήμονες αποδίδουν την αυξημένη επίπτωσή της στη ραγδαία αύξηση της θερμοκρασίας. Μάλιστα, υποστηρίζεται ότι η νόσος είναι επακόλουθο της κλιματικής αλλαγής. Συγκεκριμένα, φαίνεται πως καθοριστικός είναι ο ρόλος των επαναλαμβανόμενων επεισοδίων αφυδάτωσης, κατά τη διάρκεια της πολύωρης και κοπιαστικής εργασίας, τα οποία οδηγούν σε ισχαιμία των νεφρών, αντιδραστική φλεγμονή και τελικά, ίνωση αυτών. Επιπροσθέτως, η ραβδομυόλυση, η τακτική χρήση σακχαρούχων ποτών και μη στεροειδών αντιφλεγμονωδών, που συνηθίζεται από τους εργάτες γης, επιδεινώνουν περαιτέρω τη νεφρική βλάβη. Τέλος, κρίσιμη είναι και η επίδραση των φυτοφαρμάκων, που χρησιμοποιούνται ευρέως στις περιοχές αυτές.

Στη Νικαράγουα, 29 αγρότες ζαχαρότευτλων, χωρίς προ υπάρχουσα νεφρική νόσο, συγκρίθηκαν με 25 άτομα που δεν εκτίθονταν σε τόσο υψηλές θερμοκρασίες (48). Η τιμή κρεατινίνης μετρήθηκε πριν και μετά τη βάρδια, για 9 εβδομάδες. Στο τέλος του διαστήματος αυτού, η μέση τιμή της κρεατινίνης των αγροτών ζαχαρότευτλων αυξήθηκε κατά 16% ($p=0.002$) και η μέση τιμή του Ρυθμού Σπειραματικής Διήθησης μειώθηκε κατά 10ml/min ($p= 0.02$). Σε μια παρόμοια έρευνα, η εργασία στο κόψιμο ζαχαρότευτλων σχετίστηκε με 20% (95%CI: 13, 27) πιο υψηλή τιμή κρεατινίνης μετά από 12 μήνες παρακολούθησης.

Έκθεση σε Φυτοφάρμακα και Χημικά

Τα φυτοφάρμακα χρησιμοποιούνται ευρέως παγκοσμίως και ειδικά στις LMICs, όπου επικρατεί έντονη επισιτιστική ανασφάλεια, λόγω της γεωπολιτικής αστάθειας και της κλιματικής αλλαγής. Υπάρχουν πάνω από 150.000 φυτοφάρμακα από τα οποία μόνο το 20% έχει ελεγχθεί για τοξικότητα. Ακόμα λιγότερη είναι η έρευνα που έχει γίνει σχετικά με επίδραση των ουσιών αυτών στο καρδιαγγειακό σύστημα. Σε μια από τις ελάχιστες έρευνες σε αυτό το πεδίο, η χρήση οργανοφωσφορικών φυτοφαρμάκων σχετίστηκε με αύξηση καρδιακών συμβάντων στην Ταιβάν και πιο συγκεκριμένα, με Σ.Κ. για αρρυθμίες και στεφανιαία νόσο ίσο με 1.25 (95% CI: 1.07, 1.39) και 1.13 (95% CI: 1.01, 1.27) αντίστοιχα.

Είναι απαραίτητο να προαχθεί μελλοντικά, η διενέργεια μελετών με στόχο να αναδειχθεί η πραγματική σχέση των χημικών με την καρδιαγγειακή νόσο, λαμβάνοντας υπόψιν παράλληλα την επίδραση των κοινωνικών προσδιοριστών της υγείας σε αυτή τη σχέση, καθώς φαίνεται ότι το οικονομικό και εκπαιδευτικό επίπεδο την επηρεάζει. Τέλος, είναι σημαντικό να αναδειχθεί ο αναδυόμενος ρόλος των μικροπλαστικών στην ανθρώπινη υγεία.

Γενική Συζήτηση και Συμπεράσματα

Μέσω αυτής της συστηματικής ανασκόπησης της βιβλιογραφίας, αναδείχθηκε ο ρόλος της ατμοσφαιρικής ρύπανσης, της κλιματικής αλλαγής και της χημικής ρύπανσης. Αυτοί οι παράγοντες αποτελούν πιθανούς παράγοντες κινδύνου για καρδιαγγειακή νόσο στις LMICs. Η ανάδειξη της σχέσης αυτής είναι σημαντική για τη Δημόσια Υγεία, καθώς πρόκειται για περιβαλλοντικούς παράγοντες, οι οποίοι σχετίζονται άμεσα με την ανθρώπινη δραστηριότητα και μπορούν να προληφθούν σε μεγάλο βαθμό. Ταυτόχρονα, αναιρείται η άποψη πως οι συμπεριφορικοί παράγοντες αποκλειστικά, επηρεάζουν την ασθένεια και δίδεται η αρμόζουσα προσοχή στο «περιβάλλον», το οποίο και αποτελεί αδιαμφισβήτητο προσδιοριστή της υγείας. Επίσης, τα κράτη καλούνται να αναλάβουν τις ευθύνες τους σχετικά με τη διαμόρφωση υγιούς αστικού περιβάλλοντος χώρου για τους πολίτες τους, μέσω εφαρμογής δράσεων πρόληψης.

Από όσο γνωρίζουμε, η μελέτη αυτή είναι η πρώτη που προσεγγίζει και τους τρεις περιβαλλοντικούς παράγοντες σε σχέση με την καρδιαγγειακή νόσο. Η ανάδειξη της σχέσης αυτής, έγινε μέσω συστηματικής ανασκόπησης της βιβλιογραφίας των τελευταίων δέκα ετών. Χρησιμοποιήθηκε αναλυτική μεθοδολογία, με αυστηρά κριτήρια επιλογής των

άρθρων. Αποσαφηνίστηκε ο ρόλος σημαντικών συγχυτικών παραγόντων, περιβαλλοντικών και κοινωνικών. Συνεπώς, μέσω της έρευνας αυτής, παρέχεται ένα πιο ολοκληρωμένο θεωρητικό υπόβαθρο για το μελλοντικό σχεδιασμό μελετών σε αυτόν τον τομέα. Ο βασικός περιορισμός της έρευνάς μας είναι πως, λόγω των διαφορετικών μεθοδολογιών και ορισμών, που χρησιμοποιήθηκαν στις επιλεγμένες μελέτες, δεν είναι ασφαλές να γενικευτούν τα αποτελέσματα που συλλέχθηκαν. Επίσης, χώρες της Αφρικής δεν αντιπροσωπεύονται στην υπάρχουσα βιβλιογραφία.

Η καρδιαγγειακή νόσος επηρεάζει δυσανάλογα τις φτωχές χώρες, όμως η σχέση αυτή δεν έχει λάβει την αρμόζουσα προσοχή σε επίπεδο έρευνας και πρόληψης στις LMICs. Συνεπώς, είναι απαραίτητο να προαχθεί και να υποστηριχθεί η έρευνα στις χώρες αυτές. Ειδικά, η Αφρικανική ήπειρος πλήττεται ιδιαιτέρως από τους περιβαλλοντικούς παράγοντες, με 32% των Αφρικανών, να εκτίθενται σε συγκεντρώσεις ατμοσφαιρικών ρύπων, που υπερβαίνουν τα όρια του ΠΟΥ. Χρειάζεται επίσης, σχεδιασμός πολυκεντρικών, προοπτικών μελετών, που θα μετρούν το αθροιστικό αποτέλεσμα της αυξημένης θερμοκρασίας και της ατμοσφαιρικής ρύπανσης και οι οποίες θα λαμβάνουν υπόψιν τους, κοινούς, αποδεδειγμένους συγχυτικούς παράγοντες, όπως συζητήθηκε παραπάνω.

Οι μελλοντικές προβλέψεις σχετικά με την κλιματική αλλαγή και την περιβαλλοντική μόλυνση είναι δυσοίωνες. Η θερμοκρασία της Γης προβλέπεται να αυξηθεί από 1.1° C ως 5.4° C μέχρι το 2100 και αυτή η αύξηση εξαρτάται αποκλειστικά από τις ενεργειακές επιλογές που θα κάνει η ανθρωπότητα στο άμεσο μέλλον. Ταυτόχρονα, η ατμοσφαιρική ρύπανση αποτελεί μεγάλη πρόκληση. Ο Παγκόσμιος Οργανισμός Υγείας έχει ορίσει τα επιτρεπόμενα όρια στις συγκεντρώσεις των ατμοσφαιρικών ρύπων, ωστόσο 98% των αστικών κέντρων, με περισσότερους από 100.000 κατοίκους, υπερβαίνει αυτά τα όρια. Τέλος, και η χημική ρύπανση φαίνεται και αυτή, να παίζει αρνητικό ρόλο στην εμφάνιση της καρδιαγγειακής νόσου. Από τα ανωτέρω, μπορούμε να συνάγουμε ότι η Συμφωνία του Παρισιού αποτελεί τη σημαντικότερη δέσμευση του αιώνα, για την υγεία. Είναι αδήριτη η ανάγκη για θεσμικές, αλλά και ουσιαστικές αλλαγές στους τομείς της παραγωγής και της ενέργειας, ενώ ταυτόχρονα πρέπει να ενσωματωθούν σε αυτές, οι κοινωνικοί προσδιοριστές της υγείας. Ταυτόχρονα, πρέπει να εμπλακούν τομείς, πέραν του τομέα της υγείας, όπως αυτοί των μεταφορών, της ενέργειας κτλ.

Είναι δηλαδή σημαντικό να ενθαρρυνθούν εναλλακτικές προτάσεις στις στρατηγικές πρόληψης της ασθένειας, οι οποίες θα είναι προϊόν διατομεακής και διεπιστημονικής συνεργασίας σύμφωνα με την αρχή του “Health in All Policies”. Οι συνολικοί στόχοι για την ευημερία και την υγεία των πληθυσμών, θα πρέπει να δίεπονται από εξατομικευμένες και στοχευμένες προτάσεις για κάθε χώρα, που θα ανταποκρίνονται στις οικονομικές και πολιτιστικές της ιδιαιτερότητες, λαμβάνοντας υπόψιν τους την οικολογική προσέγγιση της υγείας.

Abstract

Context: Cardiovascular Disease (CVD) is the leading cause of morbidity and mortality in Low and Middle Income Countries (LMICs). Conventional risk factors of CVD alone, are unlikely to justify the accelerating incidence of the disease in these countries. At the same time, air pollution, climate change and chemical pollution affect disproportionally LMICs. Therefore, it could be hypothesized that these environmental factors, constitute substantial risk factors of CVD in LMICs.

Objectives: The objective of the thesis is to assess, through current literature, the potential association between these environmental factors, and the CVDs in LMICs. Furthermore we evaluate and suggest future fields of research.

Method/ Eligibility Criteria: We conducted a systematic review of the bibliography, according to PRISMA guidelines and PRISMA Flowchart. We searched the literature, by using specific pairs of terms, in multiple databases, such as PubMed, ScienceDirect, as well as grey literature, such as WHO reports etc. We only included studies and reports from the last ten years, on adult populations, conducted in LMICs, which reported clinical outcomes of CVD and more specifically, mortality rates, emergency room visits and hospital admissions, in relation to the three environmental factors (Air Pollution, Climate change and Chemical Pollution). Only studies which presented relative risks, odds ratios etc., along with standard deviations or p-value, were included in the data evaluation.

Results: A total of 3391 articles were identified, of which 107 articles met the inclusion criteria. Both climate change and air pollution, were found to have a negative impact on cardiovascular health, increasing significantly cardiovascular mortality and morbidity in LMICs. More specifically, we found that for a Particulate Matter (PM) increase of 10μg/m^3, CVD mortality and morbidity increases ranged from 0.25% to 1.22% and 0.14% to 0.26% respectively. Stroke mortality and morbidity ranged from 1.22% to 3.43% and 1.16% to 1.37% respectively. Extreme temperatures were also related to increased mortality and morbidity rates, with inconsistent results, due to different median temperatures among the countries, as well as different definitions of “heat” and “cold”. Exposure to chemical pollution was linked to an OR= 1.25 (95%CI: 1.07, 1.39) and OR= 1.13 (95%CI: 1.01, 1.27) for arrhythmias and coronary disease, respectively.

Limitations: Diversity on exposure assessments, lack of common definitions and differences in the characteristics of the populations studied, limited the ability to generalize. In comparison to the other two risk factors, the role of chemical pollution as a potential risk factor of CVD in LMICs is under investigated and needs further investigation**.**

Conclusions: The results indicate that air pollution, climate change and chemical pollution could be important risk factors of CVD in LMICs. These findings can be implemented in public health policies.

Key Words: Air Pollution, Climate Change, Chemical Pollution, Cardiovascular Disease, LMICs

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Introduction

Rationale of the Essay and Research Questions

Cardiovascular Disease (CVD) is the major cause of mortality and morbidity worldwide. More specifically, Ischemic Heart Disease (IHD) and Stroke account for one third of deaths globally and therefore, constitute a predominant issue of Global Health (1). The majority of these deaths occur in Middle and Low Income Countries (LMICs), which experience an epidemiological transition, mainly characterized by a rapid increase in the prevalence of CVD (2). However, as most research in the field of CVDs is conducted in High Income Countries (HICs), the underlying drivers of the fast-paced epidemiological transition occurring in LMICs remain elusive.

Conventional risk factors of CVD, such as smoking and unhealthy diet, have been studied thoroughly during the last decades. However, literature suggests that the rise of CVD in LMICs cannot be attributed only to these factors (3). On the contrary, the accelerated incidence and the increasing CVD death rates imply that probably, in the context of LMICs, there are supplementary risk factors of CVD, to the classic ones, which have been poorly investigated until now. Climate change, air pollution and chemical pollution affect LMICs, in a disproportional way, compared to HICs. These environmental factors have been studied thoroughly in relation to other non-communicable diseases (NCDs) and more specifically, respiratory disease and cancer. However, there is emerging evidence, that they might play a role as substantial risk factors in other NCDs too (4).

Therefore, the overall objective of this essay is to investigate the potential association of the aforementioned environmental factors with CVD. We investigate whether there is a causal relation between CVD and environmental factors, namely, climate change, air pollution and chemical pollution in LMICs. In case such an association exists, we discuss the extent of it and we propose future fields of research. In particular, we conducted a systematic review of the literature, based on PRISMA methodology. We gathered and analyzed data from multiple data bases, such as PubMed, ScienceDirect, WHO and IPCC reports etc.

Structure of the Essay

This essay starts with the introduction, which is followed by a chapter in which the methodology of our research is described thoroughly. We continue with the main body of the essay, which consists of four chapters. In the first chapter, we describe the phenomenon of epidemiological transition in LMICs and we discuss the role urbanization and industrialization in this process. In the next three chapters, we analyze the association of CVD with air pollution, climate change and chemical pollution, through studies conducted in LMICs. Each of these chapters is followed by a brief discussion on the validity of the included studies and a short commentary on the generalizability of their results. Then, we proceed to a chapter of overall discussion, where we present an overview of our results, we mention the strengths and limitations of our research, we discuss the contribution of our study to current literature and suggest possible future fields of research.

Methodology

Research Strategy

The study was conducted in accordance with the PRISMA guidelines. We performed this study in three stages: database search, title and abstract screening, and full-text review and extraction. We searched PubMed, ScienceDirect and grey literature, such as WHO reports, IPCC reports, in order to identify studies published from January 2010 until January 2020, which examined the association of Cardiovascular Disease (CVD) with three environmental factors. In particular, we examined the relation of air pollution, climate change and chemical pollution with CVD mortality and morbidity in LMICs. The primary outcomes were Ischemic Heart Disease (IHD) and Stroke, as the most common clinical manifestations of Cardiovascular Disease. More specifically, we aimed to answer the following questions:

1. What is the association of the concentration of air pollutants with CVD mortality and morbidity in LMICs?
2. What is the association of temperature range with CVD mortality and morbidity in MICs?
3. What is the association of chemical pollutants with CVD mortality and morbidity in LMICs?

Published literature was searched for in PubMed with Medical Subject Headings (MeSH), “Air Pollution AND CVD”, “Particulate Matter AND CVD”, “Climate change AND CVD”, High Temperature AND CVD”, “Extreme Heat AND CVD”, “Chemical pollution AND CVD”, “Agrochemicals AND CVD” etc. This search yielded 3391 published articles. We included studies involving humans, which came with an abstract and were conducted in LMICs. Countries were defined as LMICs, according to the World Bank. The titles and then the abstracts of all the articles were screened for contextual relevance to our research question. Those with a substantial content relevant our three questions listed above were included for a review.

Selection Criteria

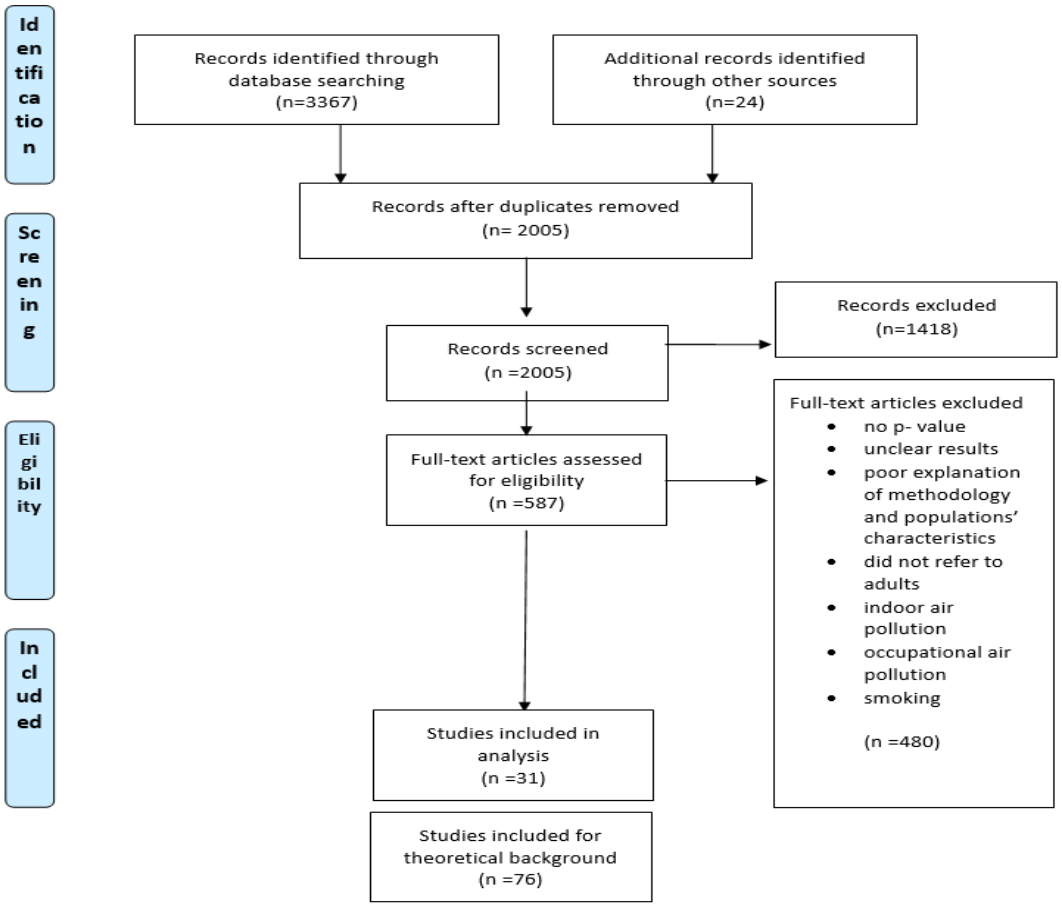
We included studies if they met the following criteria: reported clinical outcomes of CVD and more specifically mortality rates, emergency room visits and hospital admissions, according to national health data or hospital data. We included studies conducted in LMICs, according to the World Bank. The outcomes had to be associated, clearly, to at least one of the following exposures: Temperature, PM, O_3, CO_2, NO_2, SO_2, and duration of exposure to chemicals. Each study included a quantitative measurement of temperature or air pollutant's concentration, used to characterize the exposure. In the case of chemical pollution, the studied variable was the duration of exposure. The "nonlinear model statistical analysis" was used in the time series studies. This methods shows the effect of exposure event to be distributed over a specific period of time, explaining the effect of the factor at different lags. It provides a comprehensive picture of the time-course of the exposure outcome relationship. We only included studies, which reported on relative risks, odds ratios etc. along with standard deviations or p-value. We included studies on adults.

Exclusion Criteria

We excluded studies which did not describe the characteristics of the studied population, did not explain the variables and their methods, did not report p-values or presented results without statistical analysis. We also excluded studies which studied indoor air pollution, occupational air pollutants, conventional risk factors of CVD and related biomarkers. Case reports and studies with self-reported morbidity were not included.

Overall, we included 31 articles for data presentation and discussion and more specifically, 16 studies for Air Pollution, 12 studies for Climate Change and 3 for Chemical Pollution. Among the other articles, 51 of them were not used in the final synthesis, but were included in our essay, in order to provide a theoretical background, contextualize our findings and comment on the collected results. We also conducted a separate search on "Epidemiological Transition in LMICs", in order to provide an epidemiological framework to our study. Finally, we also used 3 studies conducted in HICs, to compare the situation among countries with different income.

PRISMA Flow Diagram



Epidemiological Transition in LMICs

The Socio-Ecological Approach

In 400 BC, Hippocrates was the first scientist to notice the ecological basis of disease. As he said, "*whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces, for they are not all alike, but differ much from themselves in regard to their changes. Then, the winds, the hot and the cold, especially such as common they are to all countries, and then such as peculiar to each locality*". The physical environment has always been an important determinant health.

The social, material, cultural and ecological context into which human societies evolve, influences people's physical and mental development, while external, environmental factors perpetuate disparities in life expectancy and health status, among the populations (5). There has always been a dynamic interaction between human activity and local environment. This interaction is mirrored in the status of populations' health and well-being, both in an individual and a collective way. Globalization has forced this relation to extend beyond borders, creating universal needs for the populations.

Even the concept of "Global Health" evolves and expands its initial definition beyond neglected diseases. Various new concepts, such as Non Communicable Diseases (NCDs), prevention, diagnosis and equity issues, have been addressed in the last decades, towards a different approach of the concept of "health and disease" (6). The socio-ecological model goes beyond individual and biological risks and provides a multilevel approach to the identification of the determinants of health, providing an innovative framework for Public Health interventions.

Cardiovascular Diseases and Epidemiological Transition

NCDs are the main cause of mortality and morbidity, worldwide. CVD, including IHD and stroke, is the major causes of mortality and accounts for one third of annual deaths. From 1990 until 2013, the global number of deaths due to CVD, rose by 41%, causing 17.3 million annual deaths (7). CVD constitutes therefore, a major public health issue, a great challenge in a global level and an unquestionable field for research.

Until recently, CVD was considered a “western world” disease, which affected mainly the elderly. This statement was accurate at first, but the epidemiology of the disease changed gradually. In fact, CVD appears in younger age groups and more specifically it starts at the age of 40 (8). Moreover, we witness a shift of CVD’s prevalence from developed countries, to poorer, less developed countries. For example, in 2013, CVD contributed to 11.3% of all-cause mortality in sub-Saharan Africa (SSA), with an increase of 83% from 1990 to 2013. More particularly, in 2013 the region contributed to 5.5% of global CVD deaths (2). Also, the region contributes to the majority of premature, CVD related deaths (9). In general, LMICs are presented to have lower death rates than HICs, but this observation must be interpreted with caution, because the population in LMICs is much younger than in High Income Countries (HICs) (10). After considering the average age difference of the populations, with the process of “age-standardization”, death rates are higher in LMICs than they are in HICs. This relation is very obvious in the case of certain tropical countries (Figure1). This method applies for most diseases aggravating with aging, but in the case of stroke and IHD, we observe the greatest gap.

The prevalence of CVD is also very high in countries of South-East Asia, sub-Saharan Africa, Latin America and the Caribbean. Of the 25.3 million deaths in these four tropical regions in 2016, there were 14 million deaths attributable to NCDs. In south Asia, there was an increase of 97% in deaths due to CVD, from 1990 to 2013, while for example, in Bangladesh, the mean age for IHD is only 51.9 years old, which is 8 years lower than non-South-Asians (11).

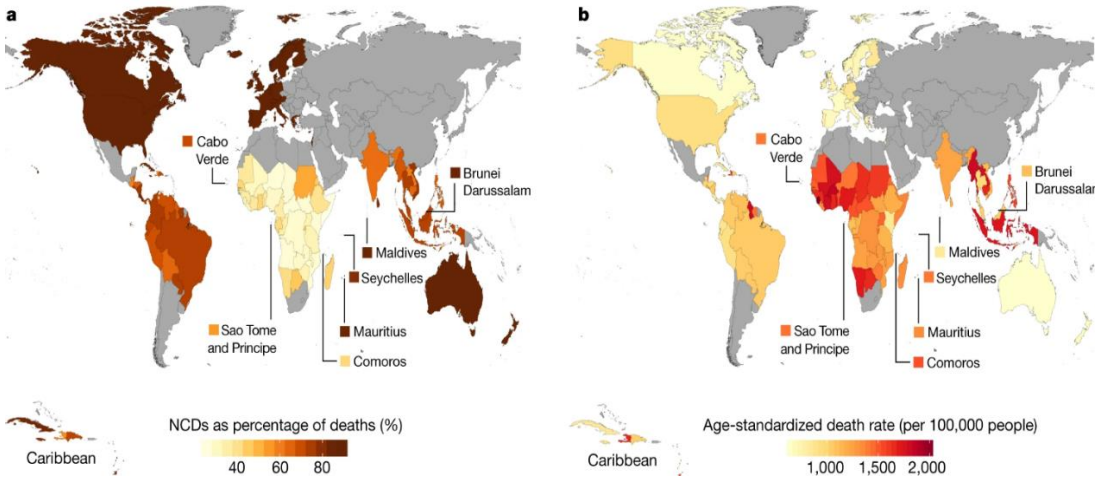


Fig.1: NCD Mortality in Tropical LMICs and HICs in 2016: Share of Deaths (a) and Age-standardized Death rates (8)

Therefore, we recognize that there is an unequal distribution of cardiovascular burden among the poorest countries of the world compared to the HICs. This poses an additional economic burden to their already stretched health systems, but it also impacts the country's productivity, as it affects young adults. India is considered as the country with the greatest potential loss in productive years of life, because of deaths attributable to CVD, in people 35-64 years old. Future projections suggest that this loss will increase in the future and more particularly, it is estimated to be 940% higher than the corresponding loss in the United States of America (12).

The acceleration in the epidemics of LMICs is propelled by a variety of factors, mostly demographical, historical and social. Low fertility rates, population's aging, urbanization and industrialization are the main determinants of epidemiological transition, as they change dramatically the patterns of living (6). According to Omran's model, LMICs have entered the third epidemiological stage, meaning the stage of "manmade diseases" (13). In the Eastern Mediterranean region, the Arabic spring uprising, revolutions and wars have transformed the demographic patterns. Life expectancy rose from 65, to 71 years old in only 13 years, while during the same period of time, IHD, the leading cause of mortality in the region, increased by 17.2% (Figure 2*).* The environment plays a crucial role in the transition in the area, where extremely high temperatures are recorded, creating food insecurity (14).

Epidemiological transition is also promoted by changes in the nutritional status of the populations. More particularly, rates of increase in obesity's prevalence in adults in Asia, Africa and Latin America are 2-5 times higher than in the United States of America (15). However, there are exceptions, as some LMICs follow the *"protracted or prolonged element",* because of the coexistence of infections and NCDs. Africa for example, bears the double burden of Diabetes Mellitus (DM) and Tuberculosis. Moreover, we should highlight the *"epidemiologically polarized element*", caused by social inequalities. Undermined populations could remain in the second stage, this of "The Age of Pestilence and Famine", with high rates of death, due to malnutrition and infections (16).

In 2014, 54% of the world's population lived in urban regions and this percentage is expected to rise to 66% until 2050. Accelerated urbanization is observed mostly in Africa and Asia and is it caused by the sudden economic development combined with agricultural insecurity and ecological disasters, due to climate change. Urbanization is also related to population's growth, forced migration, because of wars and political instability and to the existence of greater economic and educational opportunities in the cities (17). All these

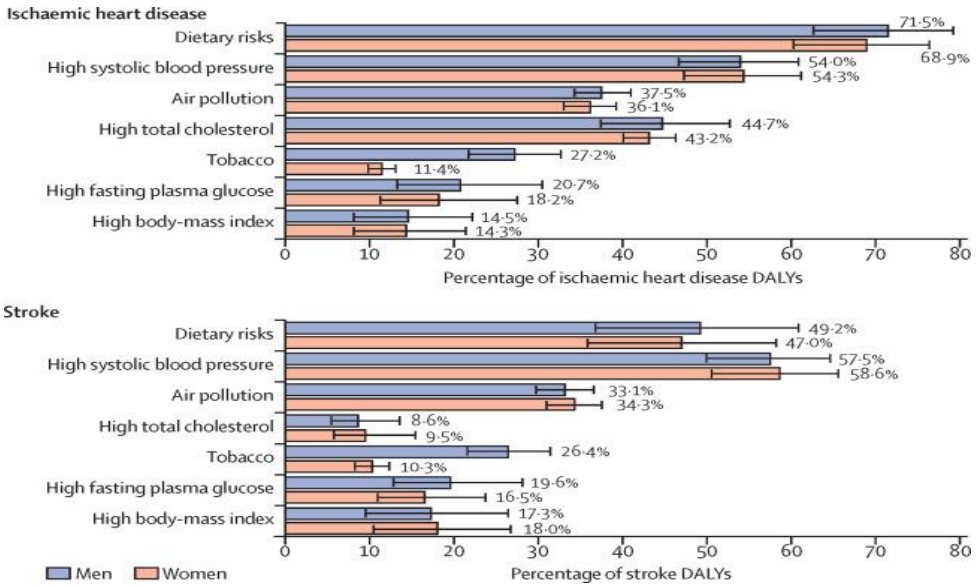
contributing factors arise simultaneously, forcing the transition to happen in a massive, rapid way. Latin America, for example faced in a relatively short period of time three demographic shifts. There was an important increase in life expectancy combined with population's growth and extremely rapid urbanization, with 90% of the population living in cities (18).

Also, urbanization is an important social process, because it establishes new dynamics in human society, and it is undoubtedly impactful in the 21st century. We experience an unprecedented urbanization, especially in LMICs, which causes remarkably big changes in human life. Urbanization not only transforms the environment people live in, but it also urges people to alter their lifestyle, which according to many researchers, is a key determinant of health (19). In a way, lifestyle choices represent the way people perceive and understand their health and as a result, take decisions in order to maintain it. Urbanization promotes changes in dietary and physical activity patterns, increases automobile use, it encourages social isolation and overcrowding. These are well-studied, behavioral risk factors, which derive from the modern way of living.

Behavioral factors are not the only drivers for the increasing incidence of CVD. Urbanization and industrialization are the main characteristics of the 21st century and they influence human behavior, as mentioned above. At the same time, they both contribute to environmental pollution and climate change, which are recognized as major risk factors for NCDs (20). Until now, most prevention programs focus on the four conventional, behavioral risk factors of CVD, meaning smoking, use of alcohol, unhealthy diet and lack of exercise (1). More particularly, CVD prevalence increase in LMICs has been explained only by changes in lifestyle patterns in these countries, as a result of globalization (21). However, the rapid increase in CVD mortality implies that there could be other equally important drivers. Pollution and climate change could contribute to a percentage of the million annual deaths from CVD in LMICs. In a global level, the risks that caused the fastest rise of NCDs between 2010 and 2016, were the lack of physical activity, followed by ambient air pollution (AAP) (22).

Another examples is India, one of the booming economies, which has experienced the creation of industrial cities, which caused fundamental social and environmental consequences (23). The average life expectancy increased from 41 years old to 61 years old in 30 years (24). India is only one of the many examples of the influencing role of the environment on the prevalence of CVD. Nevertheless, the situation has not been addressed properly until now (25).

Some researchers embrace the idea that urbanization has an effect on gene expression, probably in the context of the environmental factors' effect on post-translational modifications. In some studies, populations with urban lifestyles, where found to have some modifications of the gene expressions in the peripheral blood, compared to populations in rural areas (26),(17). These alterations in gene expressions were attributable to biotic factors and lifestyle and promoted several pathways, such as inflammation pathways or hypertension-related proteins. This implies that urbanization influences transition in multiple ways.



Percentage contribution of major risk factors to ischemic heart disease and stroke DALYs in India by sex, 2016 (25)

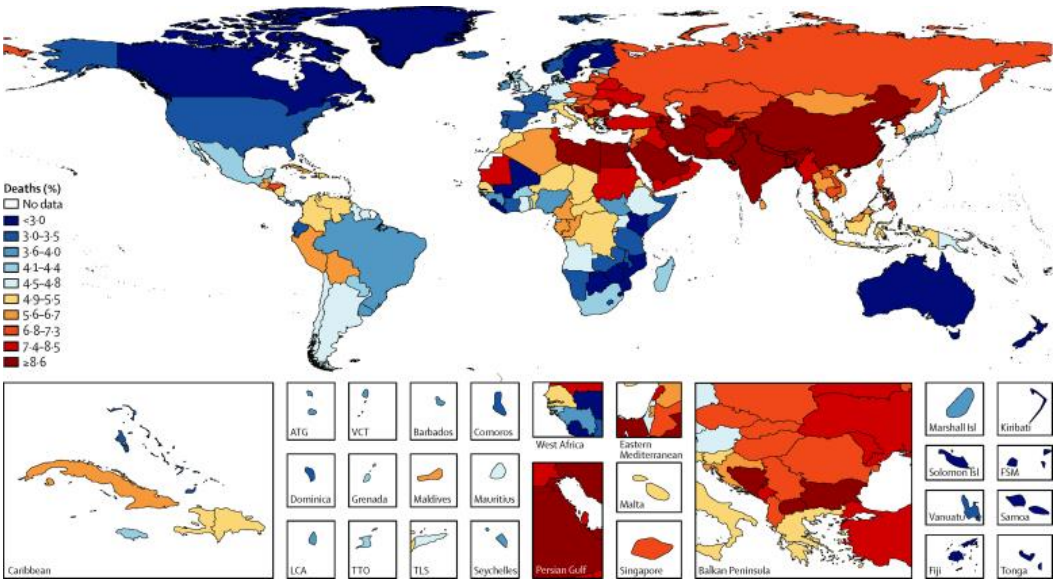
Air Pollution and Cardiovascular Disease

Geography and Epidemiology of Air Pollution

Air pollution constitutes a major threat for the populations and an important issue for Public Health, globally. Household and ambient air pollution (AAP) combined, kill almost 7 million people each year, according to the WHO. This accounts for 16% of all deaths and more particularly, three times more than the deaths due to malaria, tuberculosis and HIV, combined and even fifteen times more than the deaths attributable to wars (9). These deaths are considered premature and they could have been prevented. More specifically, the majority of the deaths attributable to AAP, are caused by NCDs. Air pollution alone was responsible for 5.6 million NCD related deaths in 2015 (27), while according to WHO' s estimations, in 2016 stroke and IHD were accountable for 58% of the deaths related to AAP. Overall, AAP constitutes the fifth major risk factor for NCDs, as mentioned in the declaration of the United Nations General Assembly (21).

AAP is related to rapid and uncontrolled urbanization and industrialization. According to the latest reports, 80% of urban areas of the planet exceed the WHO air quality guidelines. Most of these areas are located in LMICs (28). China, with a booming economy and one of the fastest growing industries in the world, is a good example of the association between industry and air pollution. The country's rapid economic growth has led to high levels of industrial waste, with 5000 billion kg annual emission of carbon dioxide ($C0_2$). The economy depends strongly on coal consumption, which is responsible for 64% of domestic energy consumption in the country (29).

The situation is similar in other countries which have been relying on their industries during the recent years. India, Pakistan, as well as other countries of the Southeastern Asia and of Western Pacific are the regions where the highest levels of AAP are met. In fact, 91% of all premature deaths, attributable to AAP, occur in these regions. South and East Asia alone, had 59% of the 4.2 million $PM_{2.5}$ related deaths in 2015 with1.36 million deaths (CI:1.19 million,1.56 million) in South Asia and 1.14 million deaths (CI: 0.97 million,1.31 million) in east Asia (30). In LMICs air pollution is associated to a plethora of negative effects, which range from increasing morbidity and mortality, to great economic damage.



Map 1: Deaths attributable to long-term exposure to PM2.5 in 2015 (8)

In a big part of the world, pollution is increasing rapidly. Even though indoor and water pollution, which are mostly related to extreme poverty and lifestyle, are decreasing, AAP, mostly produced by industry, electricity generation and agriculture, rises quickly (9). The phenomenon is more obvious in LMICs, where uncontrollable industrialization and rapid urbanization take place. More specifically, 97% of their cities with more than 100.000 people, exceed the WHO guidelines. This percentage is twice as big as the one observed in HICs, where only 49% of the cities don't meet the WHO standards (27).

Particulate Matter (PM) levels increased by 8% from 2010 to 2016 (31). Global population-weighted $PM_{2.5}$ refers to the average level of an exposure of a population to $PM_{2.5}$ and it increased by 11.2% from 1990 (39.7μg/$m^{3)}$ to 2015 (44.2μg/m^3), especially during the last five years. The two most polluted countries in 2015 were Qatar (107.3μg/m^3) and Saudi Arabia (106.2μg/m^3). Between the LMICs, the highest concentrations were noticed in Egypt (104.7μg/m^3), followed by Bangladesh (89.4μg/m^3), Mauritania (85.1μg/m^3), Libya (79.2μg/m^3), Nepal (75μg/m^3), and India (74.3μg/m^3). At the same time, between the countries with the largest populations, we notice that since 2010, exposure to air pollutants increased in most of them, with Bangladesh and India experiencing the greatest increases (Table 1) (32). Population weighted Ozone was also increased by 7.2% during the same period, with the biggest increase being witnessed in China, India, Pakistan, Brazil and Bangladesh.

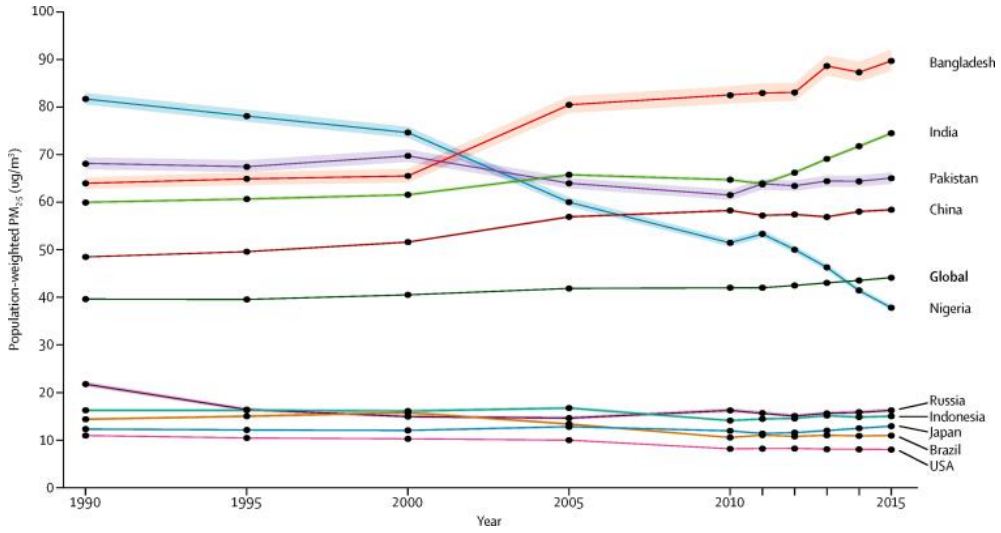


Table 1: Population Weighted PM2.5 from 1990 to 2015 (9)

Despite the accelerating incidence of CVD and the high exposures to air pollution, scientific evidence from LMICs is limited. LMICs are exposed to significantly higher levels, due to rapid and ill-regulated industrialization, while they lack inadequate enforcement of environmental legislation. At the same time, because they share different lifestyles, cultures and epidemiological patterns of conventional risk factors than developed countries, generalizability of findings from HICs, is insufficient.

Description and Pathophysiology of Air Pollutants

Air pollution can be ambient or indoor Household air pollution is seen mostly in LMICs, as a result of burning fuels in inefficient stoves or open hearths. For the purposes of this essay, we are going to focus only on the effect of AAP, which mainly derives from human activity. The most common human sources are fuel combustion from motor vehicles, heat and power generation, industrial facilities (factories, mines), agricultural waste sites and waste burning (33). Data from urban measurements, show that 25% of PM results from traffic,15% from industry, especially electricity generation and 20% from domestic burning of fuels (21).

The most harmful pollutants are PM, Ozone, Black Carbon, Carbon Dioxide ($C0_2$), Nitric Oxide (NOx). PM is a complex mixture of inhalable particles, which consist of nitrates, black carbon, mineral dust and ammonia. Those with a diameter of less than 10 microns (PM_{10}), also called “thoracic particles” and those with a diameter or less of 2,5 microns (PM2.5), also called “fine particles”, have the worst impact on human health (33). PM_{10} and $PM_{2.5}$ are products of mechanical processes, like construction, while PM less than 2.5

microns are basically produced through combustion. According to their diameter, they tend to have different physiological behavior. PM_{10} cannot penetrate beyond the extra thoracic region of the respiratory system, while $PM_{2.5}$ enters smaller airways and alveoli and penetrates the systemic circulation. Particles with a diameter less than 0,1microns, or else “ultrafine particles”, are products of diesel and gasoline combustions. They also able to penetrate the bloodstream and favour stroke and IHD. Interestingly, some regions of the Eastern Mediterranean and Africa are often affected by natural desert dust particles, whose impact on the cardiovascular system is similar to the impact of the ultrafine particles (20).

Ground-level Ozone is a very harmful pollutant too. It is a basic component of photochemical smog and it is produced by a secondary chemical reaction, leading to the creation of additional pollutants. Also, Black Carbon, apart from its contribution to global warming, is also a component of $PM_{2.5}$. It comes from fossil fuels, biofuel and biomass and compared to Carbon Dioxide, it has a very short period of life, from days to weeks, which means that reducing its concentration, would have an immediate effect on Public Health (33). Finally, there is also Sulfur Dioxide, a product of industrial activity, mainly produced by generations of electricity from coal, oil, but also vehicle emissions (34).

Short term exposure to air pollutants is the exposure with duration less than 24 hours, while long term exposure is the exposure during one year. According to the duration of the exposure, different cardiovascular outcomes occur. Generally, acute exposure increases the incidence of myocardial infraction, acute heart failure and arrhythmias, while chronic exposure is blamed to pose even greater risks to the cardiovascular system. Nevertheless, the exact pathophysiological mechanisms involved are not understood in depth. The most supported hypothesis describes the dominant role of oxidative stress and inflammation, promoted by PM, which is the most studied of all pollutants (20). After entering the systematic circulation, ultrafine particles combine with proatherogenic molecules, enhancing the creation process of atherogenic plaques (35). It is well established that atherosclerosis is a major risk factor for ischemic heart disease and cerebrovascular events.

Long term exposure to particles induces tissue oxidative stress, through the release of pro-inflammatory mediators from the lungs, such as IL-6 (35). As a result, inflammatory cytokines, lipids, and macrophages “spill over” into the circulation, leading to an inflammatory state, which in its turn, promotes hypercoagulability, dyslipidemia and thrombosis (20). Literature suggests that short term exposure to diesel particles is directly linked to acute myocardial infraction, because diesel particles contact directly with platelets

and provoke rapid platelet sensitization in the vessels (36). The same mechanisms are also involved in stroke. This exact state of increased thrombosis is the reason why short term exposure to air pollution causes mostly myocardial infraction with “ST- Elevation”, rather than “Non ST- Elevation” and more ischemic strokes than hemorrhagic strokes (37). Pollutants have been also shown to provoke imbalance of the autonomous system and more specifically, sympathoadrenal activation, in both acute and chronic settings. Some studies even suggest there is an association of increased sympathetic tone, with ventricular arrhythmias and sudden death (37). Moreover, particles promote alterations, which contribute to the instability of the atherogenic plaques and to the increase of blood pressure (38), (39).

Air Pollution and Cardiovascular Mortality

Most national studies from LMICs come from China, which struggles with very high levels of pollution, being the world’s second largest economy and the biggest producer and consumer of coil (40). Research has also been conducted in other countries which struggle with high levels of AAP, such as Iran, Brazil, India etc. That being said, we will now discuss the association between air pollution and CVD mortality and morbidity in these regions.

Nanjing is a city of 8.27 million habitants, located in the Yangtze River Delta and it is one of the most polluted areas in China. In a study conducted from 2014 to 2016, long term exposure to PM was associated to health burden (41). As expected, PM levels where higher than the WHO guidelines (45μg/m^3) and their peaks where observed during rush hours. In this study, stroke was the leading cause of mortality, followed by IHD, lung cancer and COPD. In 2016, stroke contributed to 44% of the $PM_{2.5}$ related deaths and IHD to 28%. Death rates in the elderly were higher. In a study with similar methodology, in Varanasi, India ambient $PM_{2.5}$ exposure caused 5700 premature deaths from 2003 to 2015, of which 29% was attributed to IHD and 18% to stroke (42).

In a cohort study, conducted from 2010 to 2012, in Beijing, the daily mean $PM_{2.5}$ concentration was 96.2μg/m^3, ranging from 3.9μg/m^3 to 493.9μg/m^3. The results showed a non-linear dose-response relationship, with a steeper function of the mortality curve at lower concentrations (Fig.3) Overall, a 10μg/m^3 increase of $PM_{2.5}$ was found to cause an average increase of 0.25% (95%CI: 0.16, 0.34) in IHD morbidity and 0.26% (95%CI: 0.03, 0.49) in IHD mortality (43).

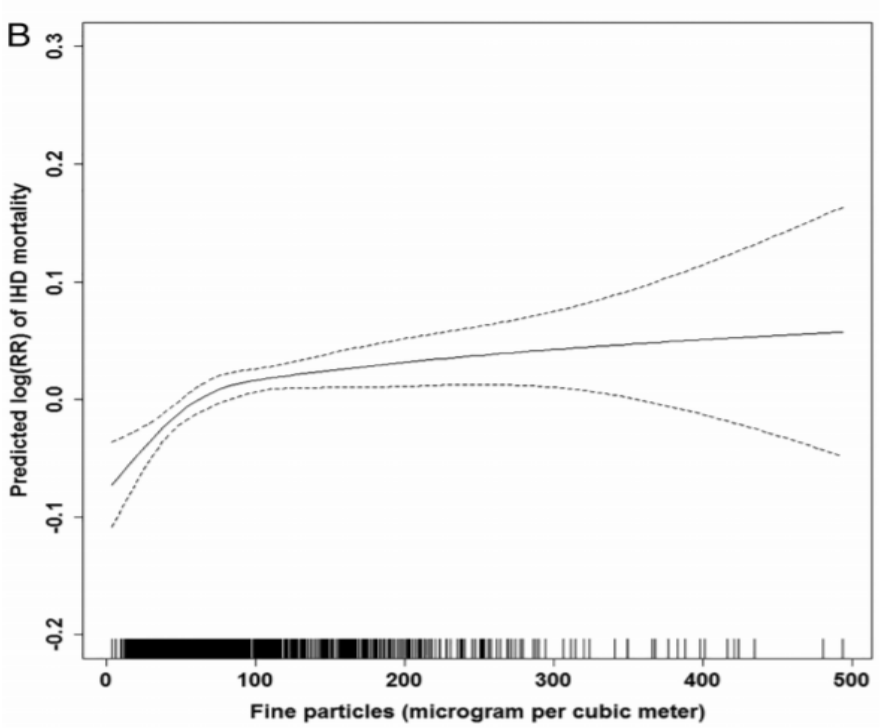


Fig 3: Association of PM concentration with CVD Mortality (43)

Lanzhou is an industrial city, which hosts many metallurgical and petrochemical industries. It is one of the most polluted cities in the China. A times-series study was conducted, where PM levels were related to CVD deaths on different days. The effects of exposure to environmental factors change with time. Mortality rates can be different throughout a period of time, after the initial exposure. This is why, the effect of the studied variable is recorded in different lag days. A 10μg/m^3 increase in PM levels was related to an increase of stroke mortality per 1.22% (95%CI: 0.11, 2.35) at lag4, where the delayed effect reached the maximum. The only statistically significant result was observed at lag0, where a 10μg/m^3 increase of $PM_{2.5}$ levels, was associated to a rise of IHD mortality by 0.47% (95%CI: 0.06, 0.88). Again, the curve of dose-response was steeper in low concentrations (44).

In a study conducted in Mexico, daily mortality records for cardiovascular and cerebrovascular causes were obtained and compared to $PM_{2.5}$ levels, from 2004 to 2013 (45). An increase of 10μg/m^3 was associated to increased cardiovascular mortality by 1.22% (95%CI: 0.17, 2.28) and cerebrovascular mortality by 3.43% (95%CI: 0.10, 6.28). The results were not statistically significant for neither of the studied variables. Moreover, the writers underline the fact that when they defined the lags, unlike other studies, they

used the date of death rather than the day of the apparition of the first symptom. Moreover, they also mentioned that meteorological conditions were not taken into account.

A multicity cohort study, with 70.947 middle aged participants, took place in China from 1991 until 2000 (46). Long term exposure to several pollutants was studied in relation to CVD mortality, using proportional hazards regression models and after adjusting for many individual risk factors. During the nine years, the average concentrations of PM, SO_2 and NO were 289, 73 and 50 μg/m^3, respectively. An increase of PM, SO_2 and NO by 10μg/m^3 corresponded to 0.9% (95%CI: 0.3, 1.5), 3.2 (95%CI: 2.3, 4.0) and 2.3 (95%CI: 0.6, 4.1) respectively in CVD mortality (Chart 1).

Air Pollution and Cardiovascular Morbidity

Pakistan's population grows rapidly. It has increased by 97millions from 1990 until 2017. Most of the people live in urban areas, such as Karachi, an industrial city, which is the fourteenth largest city in the world, with more than 3 million vehicles on its streets. In a time-series study, PM constituents were related to the number of admissions, due to cardiovascular disease, from 2008 to 2009 (47). Nikelium and Aluminum were associated with an increase in the risk of CVD hospitalization. The retalive risk was 1.14 (95%CI:1.04,1.25) for Nikelium and 1.21 (95% CI:1.03,1.43) for Aluminium.

In Beijin, pollution sources are mainly the industries of the suburban areas, the rapid rhythm of coal burning and vehicle emissions. In 2013, the number of vehicles was almost 5.43 million. In a study conducted in Beijing, data on Emergency Room (ER) visits were selected from 10 hospitals and were associated to daily $PM_{2.5}$ concentrations (48). The daily mean concentration of $PM_{2.5}$ was 101.1μg/m^3 and the total number of cardiovascular visits was 56.221. Results showed that an increase of $PM_{2.5}$ per 10 μg/m^3, was associated to an increase in ER visits by 0.14% (95%CI: 0.01, 0.27) at lag3. More specifically, IHD's risk increased by 0.56% (95%CI: 0.16, 0.95), while the risk for arrhythmias increased by 0.81% (95%CI: 0.05, 1.57). The results did not change when they were evaluated in two-pollutant models, meaning when they were adjusted to concentrations of O_3, CO, NO_2, and $S0_2$. This fact strengthens the hypothesis that PM has an independent impact on cardiovascular morbidity. In another study from China, 24.845 adult Chinese residents of a heavy industrial area, participated in a large population-based, cross sectional study, in order to examine the association of air pollution with stroke (49). Increases on PM_{10} and

$S0_2$ by 10μg/m^3 caused an increase of ischemic stroke by 1.16 (95%CI: 1.03, 1.30) and 1.14 (95%CI: 1.01, 1.29) respectively.

Even though there has been some research on the association of air pollution with stroke morbidity, the results of the studies are not consistent. Some studies failed to find significant results on CVD mortality, such as the BAPHE study in Lebanon (50). A nationwide time series study was conducted to analyze the effect of air pollution on ischemic stroke morbidity in China (51). China bears the greatest burden of stroke (52). This study used data from 0.28 billion people from 172 cities. A 10 μg/m^3 increase in $PM_{2.5}$, $S0_2$, $N0_2$, 0_3 and a 1 μg/m^3 increase in CO were associated with 0.34 (95%CI: 0.20,0.48), 1.37 (95%CI: 1.05, 1.70),1.82 (95%CI: 1.45, 2.19), 0.01 (95%CI: -0.14,-0.16) and 3.24 (95%CI: 2.05, 4.43) increase in stroke morbidity, respectively. The associations of $S0_2$ and NO_2 remained significant in two-pollutant models (Chart 2). An interesting observation is the fact that there were smaller effects of air pollutants in cities with higher levels of pollution. One possible explanation could be “harvesting mortality” or else called, “mortality displacement”, which means that in cases of extreme conditions, vulnerable groups die soon before the peak of the phenomenon. In this case, more vulnerable individuals would die before the concentration levels reached really high levels.

In one of the few cohort studies conducted in LMICs, long term exposure to air pollutants was associated with stroke morbidity. Six LMICs were included in the study and more specifically, Ghana, India, China, Mexico, Russia and South Africa (53). The mean $PM_{2.5}$ concentration in the six countries was 23.09μg/m^3 with China having the highest level, of 32.79μg/m^3, followed by India with 30.69μg/m^3. Africa had the lowest level, with 5.93μg/m^3. After adjusting for possible confounding factors (age, sex, physical activity, etc.), the Odds Ratio score was 1.13 (95%CI: 1.04, 1.22) for an increase of $PM_{2.5}$ by 10μg/m^3. PM contributed to 6.55 (95%CI: 1.97, 12.01) of all stroke cases. The overall dose-response curve was steeper in lower concentrations (Fig 3).

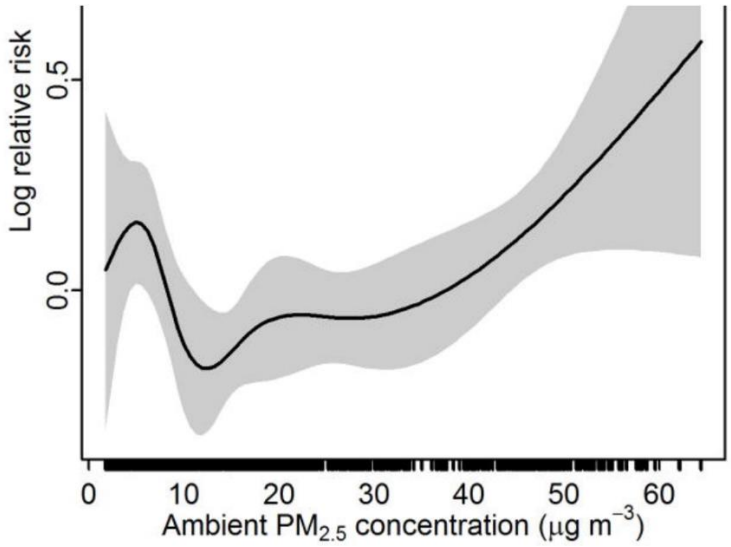


Fig 3: Concentration-Response Curve for the effects of ambient PM2.5 on stroke for overall population in six LMICs (53)

The next study attempted to examine certain modifiers, which are some of the conventional risk factors for stroke. The modifiers which were evaluated individually were physical exercise, smoking and consumption of fruit. The study revealed higher Odds Ratios for stroke morbidity, among people who exercised a lot and were not smokers. The Odd Ratio was OR=1.20 (95% CI: 1.07, 1.35) and 1.16 (95% CI: 1.05, 1.27) respectively. These results should be interpreted with caution. One possible explanation would be that people with higher levels of outdoor physical activity are more exposed to air pollution, in the same way that non-smokers are more likely to have higher physical activity levels, hence more time of exposure to AAP.

Results from Reviews

There are not many multicity, large-scale studies on the association of air pollution with CVD mortality. APHENA is a combined European and North American study. It is interesting to compare its findings with those derived from studies in LMICs. The study uses data from the European APHEA (Air Pollution and Health: A European Approach) and the United States (“National Morbidity, Mortality and Air Pollution Study”) studies, along with data from Canada. It is one of the biggest recent studies conducted in HICs. The results on CVD mortality were significant among people older than 75 years old, where a 10μg/ m^3 increase on PM10, increased the number of deaths by 1.30% (95% CI, 0.19–2.40%) in Canada, 0.47% (95% CI, 0.23–0.70%) in Europe, and 0.51% (95% CI, 0.29–0.73%) in the

U.S.A. The estimates for CVD mortality among people under 75 years old, were positive but not statistically significant (54). It is also important to underline that cities with higher percentage of unemployment were associated with a greater impact of PM_{10} on all-cause mortality.

CAPES on the other hand, is a large multicity study in China, which combines data from sixteen cities and 96 million people (40). A 10μg/m^3 increase in PM_{10} was associated to an increase of all-cause mortality by 0.32% (95%CI: 0.28–0.35%) and of CVD mortality by 0.43% (95%CI: 0.37–0.49%). People over 65 years old, as well as people with preexisting cardiopulmonary disease and diabetes, were more vulnerable. Higher mortality risk estimates were also linked to low educational status. Now, most of the Latin American capitals exceed the WHO standards for $PM_{2.5}$ and PM_{10}, with Bogota and Lima having the highest annual concentrations of 35.1μg/m^3 and 31.5μg/m^3 respectively (55). The ESCALA project is a study conducted in Latin America. Mexico, Chile and Brazil and includes data from nine cities (56). The results of the meta-analyses confirm the significant relationship of PM and CVD. The percentage increase in CVD mortality was 0.72% (95%CI: 0.54, 0.89).

In a review in LMICs, which includes 5 countries, long term exposure of $PM_{2.5}$ was associated with cardiometabolic morbidity and mortality in LMICs. Data from Brazil, Bulgaria, China, India, and Mexico were included (57). Of all the studies on mortality, six were conducted in China, and the others were carried out in Mexico, India, and Brazil. In a national prospective study in China, for every 10μg/m3 increase in $PM_{2.5}$, the hazard ratio for CVD mortality increased by 1.09 (95%CI: 1.08, 1.10) for a six year period. In a time-series study in Guangzhou for every IQR increase (meaning an increase by 12.4μg/m3) the excess risk was 6.11% (95%CI: 1.76, 10.64). In Beijing, they found that for every 10μg/m3 increase in $PM_{2.5}$, CVD mortality increased by 0.24% (95%CI: 0.05, 0.43), and more specifically, IHD mortality rose by 0.22% (95%CI: 0.06, 0.50), while stroke mortality rose by 0.23% (95%CI: -0.03, 0.50). In Shenyang the CVD mortality increased by 0.42% (95%CI: 0.10, 0.73).

The Mexican study reported that for every 10μg/m^3 increase in $PM_{2.5}$, there was a 3.4% (95% CI 0.67, 6.18) increase in CVD mortality, while the only study from India reported 5700 (95% CI 2800, 7500) annual premature deaths attributable to $PM_{2.5}$ exposure, of which 29% and 18% were IHD and stroke, respectively. The study from Brazil showed that every 10μg/m^3 increase in $PM_{2.5,}$ the relative risk was 1.81% (95% CI 0.03, 3.61) for CVD mortality. As for morbidity, in the Brazilian study the relative risk was 2.64 (95% CI 1.60, 3.69) for hospitalizations related to $PM_{2.5}$ over a period of 10 days.

Discussion

Most of the studies included, are time-series studies. $PM_{2.5}$ and PM_{10} are the most studied variables. All of the studies found a positive relationship between pollution levels and CVD morbidity and mortality and some of them presented statistically significant results. For a PM increase of 10μg/m^3, CVD mortality and morbidity increases ranged from 0.25% to 1.22% and 0.14% to 0.26% respectively. Stroke mortality and morbidity ranged from 1.22% to 3.43% and 1.16% to 1.37% respectively. The results from reviews and metanalysis where in accordance with the results from original data. Furthermore, the exposure-response curves had the same pattern, that of a steeper line in lower concentrations, suggesting that increases in the lowest levels of PM have a greater effect on CVD mortality. This observation could apply to the theory of "harvesting mortality".

Even though the Odds Ratios of mortality and morbidity do not differ substantially between the selected studies, generalizing the results would not be safe. More specifically, the ORs represented mortality rates from different lag-days. Moreover, for mortality rates, it was not clear in all studies, whether the lag corresponded to the day of the apparition of the first symptom or to the day of death. Furthermore, there were some studies, which did not take into account the meteorological conditions in the studied region, such as humidity or temperature, even though there is strong evidence that they both alter the effect of air pollutants (58). Finally, the studies used different analysis methods. In some cases, the original results were also run on two-pollutant models and the initial positive association between PM and CVD mortality remained significant, supporting the knowledge on the strong impact of PM on health. In other studies, such an analysis was not presented, harshening the ability to generalize findings with safety.

In addition, pollutants' levels were estimated from monitoring-stations in specific spots of the cities. It is known that because of interurban variability and spatial heterogeneity even among small regions, the bias of "exposure misclassification" exists (59). More particularly, subpopulations, even within the same city, could be exposed to different pollution levels. Also, populations are proven to have dissimilar levels of responsiveness to environmental factors (60). This matter should be taken into consideration in future studies, because it implies that individuals respond differently when exposed to pollution. Furthermore, aspects of lifestyle, cultural, personal characteristics, or pre-existing medical conditions, may enhance the adverse effects of AAP on health and as a result, they should be taken into account in future studies, as potential confounding factors (40). Finally, some studies found different ORs for subpopulations with lower

socioeconomic and educational status. Socially vulnerable groups were found to present higher risks of mortality, when exposed to the same pollution levels with people with higher socioeconomic status. This finding suggests that social determinants of health could play an influencing role on air pollution's impact on CVD health and therefore, they should be taken into consideration in future research.

Climate Change and Cardiovascular Disease

Climate Change as a Public Health Issue in LMICs

In the last 130 years, Earth temperature has risen by 0.85°C, with each of the last three decades being warmer than all the decades since 1850. The rate of the temperature's increase has doubled in the last 50 years (61). Climate change and Global Warming describe the same environmental pattern, this of the consistent rise of temperature and the increasing number of extreme weather events, with short duration of climatic stability between them.

The rise of temperature in the lower atmosphere is related to the "greenhouse effect". In a way, the phenomenon is necessary, as it helps maintain the appropriate temperature on the surface of the Earth, in order to preserve life. However, at the moment, a rapid escalation of the situation is taking place, with unpredictable consequences on Earth's living creatures. Climate change is directly linked to human activity, especially to the massive burning of fossil fuels, to deforestation and to high rhythms of agricultural production. These procedures release high concentrations of carbon dioxide and other gases, which trap additional heat on the surface of the earth. It also crucial to underline that high temperatures also raise the level of air pollutants (62). Therefore, a vicious circle between air pollution and climate change is created, with a plethora of negative effects.

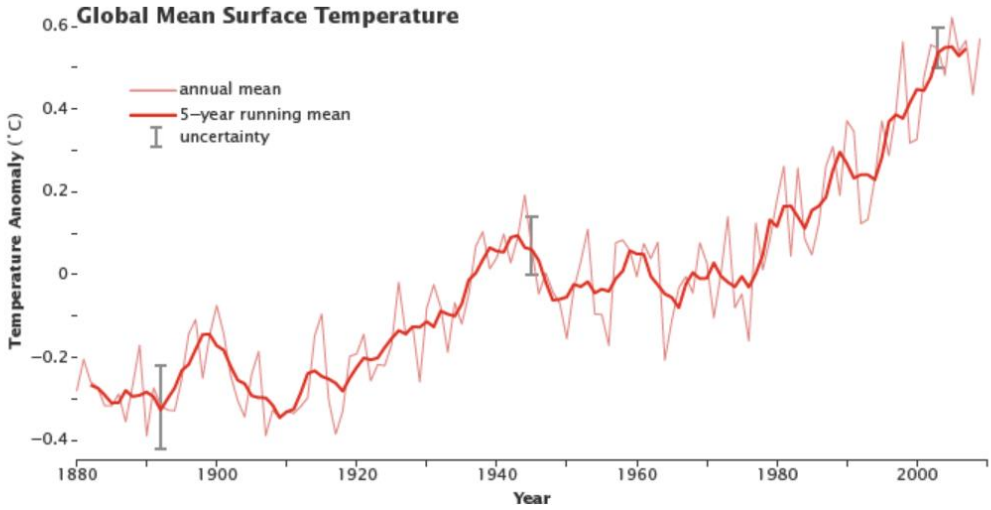


Fig. 4: NASA: Global average surface temperature, 0.5 degrees Celsius, above the long term (1951-1980) average (61)

Climate change poses multiple threats for humans, including food insecurity, water shortage, and other public health issues. It is estimated that between 2030 and 2050, climate change will cause 250.000 additional annual deaths from heat stress, malaria, malnutrition and diarrhea. This number has tripled since the 1960s and it is expected that 83.000 of these deaths will result from heat stress and will affect mostly the elderly. Annual economic damage to health systems is anticipated to be from 2 to 4 billion US dollars (63). It is well established that climate change poses great risks for Public Health, as it facilitates the spread of infectious diseases. What is less communicated, is that it also contributes to deaths from cardiopulmonary causes. The elderly, people with preexisting medical conditions, residents of megacities, of mountainous regions and people living in small islands, are among the high risk populations (64).

We should highlight at this point, that there is an asymmetry between HICs and LMICs regarding climate change. Even though rich, industrial countries are responsible for most of the carbon emissions, poor, less developed countries suffer the most from the consequences. LMICs have been always experiencing extreme weather phenomena, long periods of drought, and extreme temperatures, initially, due to their geographical location and characteristics. Nonetheless, in the recent years, they bear the burden of even more unpredictable and intense climatic conditions, because of climate change. An example of the situation in the Pacific Islands illustrates this inequity. The region is responsible for only 0.03% of the total greenhouse emissions, yet it is deeply affected by extreme weather events. At the same time, 80% of deaths in the region, were attributable to NCDs in 2017 (65). The combination of extreme climatic conditions and accelerating incidence of CVD in LMICs, as described in the first chapter, challenge their already stretched health systems.

The Effect of Temperature on the Cardiovascular System

The body reacts in multiple ways to the changes of the temperature, in order to preserve its homeostasis. The mortality induced by extreme temperatures is not always caused by hypothermia or hyperthermia, but it also relates to other, indirect causes. First of all, exposure to cold temperatures leads to high levels of catecholamine. The cardiovascular systems responds with tachycardia, vasoconstriction and elevated blood pressure. As a result, we have an increase of stroke volume, which that can lead to myocardial ischemia, especially in cases of preexisting heart condition. Additionally, it has

been proven that persistent exposure to low temperatures is an independent risk factor for the creation of atherosclerotic plaques, but also for plaque disruption (66).

Heat on the other hand, can cause great dehydration, vasodilatation and secondary acceleration of heart rate and as a consequence, increased cardiac needs in oxygen. Furthermore, heat can cause “heat stroke”, which is defined as “a form of hyperthermia associated with systematic inflammatory response, which leads to a syndrome of multi-organ dysfunction, in which encephalopathy predominates” (67). Heat stress can also induce a potential increase in blood cells counts and lead to increased blood viscosity (38). Regarding heat waves, there are two effects that have been described in literature. The first, main effect on the body is caused by the independent effect of daily temperatures, while the second, added effect, depends on the duration of the high temperatures (68).

When studying the effect of climate change on CVD mortality and morbidity, we should also take some other factors into account, except air temperature. The time within the year, the duration of the cold spells or heat waves, the interval between the extreme weather conditions, as well as other features of the surrounding environment, are all important determinants of the final health outcomes. For example, urban spaces can modify the impact of temperature on the population, due to the creation of the “urban heat island”. Urban spaces are particularly vulnerable to extreme conditions. More particularly, the surfaces of pavements and of buildings tend to absorb great amounts of heat during the day. As a result, it is possible that in such spaces, there could be a rise in urban air temperature of 2-5°C during the day and a rise of 8°C at night (69). Moreover, we should note that in cities we meet the highest levels of air pollution. Climate can affect air quality and via versa, but the combined effect of those parameters remains unclear (58).

At this point, it is critical to underline some additional factors, which should be taken into consideration, when interpreting the results of existing research. More particularly, acclimatization appears to play an influencing role. Acclimatization means that, populations used to live under certain climatic conditions and within a specific range of temperatures, gradually adapt to their local climate and respond differently to climatic stimulus, than others. In this context, local climatic conditions and characteristics could affect the mortality rates of CVD (70). Epidemiological evidence shows that populations less likely to be exposed to extreme temperatures, are more vulnerable to such changes (60). Current literature also emphasizes the role of the latitude of the studied region. In fact, latitude appears to play an important role in the process of defining the threshold temperature for the different regions of the world. For example, in the boreal hemisphere, northern countries

seem to have higher mortality rates in high temperatures, while the opposite happens with the southern countries (38).

Climate Change and Cardiovascular Mortality

LMICs suffer the most by the consequences of climate change. On top of the reemergence of infectious diseases and food insecurity, their already stretched health systems must face CVD, as an additional outcome of climate change. However, despite the imperative need for action in LMICs, most research on this topic comes from HICs.

Many studies have been conducted, in an attempt to emphasize the association between climate change and CVD mortality. One of the main issues that rise, is that are no standard technical definitions for “cold spells” and “heat waves”. For this reason, many different definitions of cold and hot are met in literature. In a study in a tropical urban city, in Puerto Rico, heat episodes were described as air surface temperature above the 90th percentile of all recorded temperatures, with a mean annual temperature at 27.2°C. For elevated temperatures, the relative risk (RR) for stroke mortality was 16.8% (95% CI: 6.81, 41.4) and for cardiovascular mortality the RR was 16.63% (95%CI: 10.47, 26.42) (71). Other studies presented different definitions. One of them, is a time series study in Thailand, where during the last 30 years, an increase of ambient temperature by 1°C, was recorded. Extremely low and high temperatures were defined according to the 1st and 99th percentiles, respectively. Temperature’s impact on cardiovascular mortality was studied for lags 0-2, 0-13 and 0-21. Extreme temperatures had a lag effect on CVD mortality, meaning that the impacts of temperature changed in different lag-days (72). The effect of extreme cold was higher at lags 0-13 and 0-21, while the effect of heat peaked earlier, at lags 0-13 and after that point, it was stabilized (Chart 3) (73). This observation suggests that heat’s effect fades with time.

In the following study, the effect of temperature on CVD mortality was studied in Brazil, in a multicity study, which included 27 cities, with 24% of the country’s population (74). The results showed a U-shaped exposure-response curve. Cold, defined as the 1st percentile, was associated to an increased RR for mortality, by 26% (95%CI: 17, 35). Accordingly, heat, defined as the 99th percentile, was related to an increase of 7% (95% CI: 1, 13). It is worth mentioning that the minimum temperature, linked to an increase in CVD mortality was higher in cities with warmer climate. At the same time, the opposite was observed for colder locations, implying that local climate and latitude play a significant role

in the definition of threshold temperature. Moreover, hot effects were found to be more immediate, but cold effects lasted longer.

Africa contributes very little to climate change, yet it is suggested that it suffers the most from its effects. In fact, it contributes to 34% of the global DALYs attributable to consequences of climate change. The Intergovernmental Panel on Climate Change (IPCC) recognizes the African continent as the most vulnerable to climatic conditions, because of its high exposures and its low capacity for adaptation (75). Few studies have been conducted in Africa and their results are contradicting. A lot of them found no association between rising temperature and cardiovascular mortality. One study, conducted in the Democratic Republic of Congo, found that temperatures above 28°C cause an increase of stroke mortality by 21%. Another study observed that a 1°C increase in temperature after the 75th percentile, is associated to 1% increase of total NCD mortality (76). A similar study in Iran though, showed 4.27% (95%CI: 0.91, 7.00) increase in CVD mortality (77).

China is also one of the countries which suffer deeply from extreme temperatures. Its mean annual temperature is projected to rise by 6,1°C from 1900 to 2100, if immediate measures for emission reduction are not taken (78). Temperatures in Tibet have been rising by 0.16°C annually, with winter temperatures increasing more rapidly than in any other region in China. A time series analysis was conducted, in order to illustrate the relationship between daily temperatures and daily mortality from cardiovascular disease (79). Low temperatures were defined by 1st percentile of temperature, relative to the 25th percentile and high temperatures were defined by the 99th percentile, relative to the 75th. For hot days, there was an increase in CVD mortality by 2.3 (CI 95%: 1.03, 5.24). The effect of cold days was not significant. Males and the elderly were found to be more vulnerable to extreme temperatures. Finally, as observed in other studies too, the effect of high temperature on mortality was found to be more immediate, but the effect of low temperatures lasted longer.

In a national assessment study in China, the effect of low temperatures on a subtropical region was studied. It is a region already vulnerable to climatic conditions. In 2008, the coldest winter of the last 100 years occurred, with temperatures 2-4°C lower than in the usual winter period. During the cold spell days, the authors observed an excess risk of 52.9 (96% CI: 42.1, 64.5) for CVD mortality and an excess risk of 54.3 (95%CI: 36.5, 74.4) for cerebrovascular mortality (80). The elderly and the females appeared to be in higher risk. A probable explanation could be that males have better thermoregulatory system, because of their hormones.

Temperature and Cardiovascular Morbidity

Vietnam is one of the countries, which is very affected by climate change. Its climate is tropical, with two seasons, one dry and one wet. Its annual temperature is projected to increase from 1.1 to 3.6°C by the end of the century. Heat waves are becoming quite common, however such weather events are not usually studied in tropical climates. The first multicity study, conducted in 25 cities in Vietnam, studied the effect of heat waves on cardiovascular morbidity (81). In this case, heat wave was defined as a temperature above the 90th percentile. The threshold was higher for the Southern cities. Heat wave was associated to an increase in cardiovascular morbidity in Northern and Southern cities by (6.8, 31.3) % and (-7.9, 3.3) % respectively. The overall morbidity was 0.8% (95%CI: -8.2, 3.6). The result is not significant, but it is worth underlying again the influencing role of the latitude. Other similar studies conducted in Vietnam, failed to reveal a relationship between high temperature and the risk of hospitalization for cardiovascular causes (82).

Other studies on the association between CVD morbidity and climate change are conducted in China. The first study is one of the few studies conducted in rural China. Ningxia Hui Autonomous Region is one of the most undeveloped regions of the country, where cardiorespiratory diseases were accountable for 30% of the total hospital admissions. The average temperature in the 203 villages that exist in the region, is 8.5°C and annual temperatures range greatly, from -18.6 to 29.7°C. Extremely low temperatures, defined as 1st percentile of temperature, were associated to an increase of 1.55 (95%CI: 1.26, 1.92) in hospital admissions. On the other hand, high temperatures, defined as 99th percentile of temperature, were associated to an increase of 1.28 (95%CI: 1.11, 1.48) of hospital admissions (83). The sharpest increase of cardiovascular admissions was observed in moderate, rather than extreme temperature changes. More specifically, moderate deviations were linked to 12.5% of total cardiovascular visits, while extreme deviations were responsible only for 0.6%. This observation could probably be attributable to the harvesting effect, even though we do not have adequate evidence from other studies, in order to support this claim.

Finally, in the urban region of Shanghai, in China another study on morbidity was conducted (84). This time, heat wave was defined as a period of at least 7 days, with daily temperature above the 97th percentile. Respectively, cold spell was defined as temperatures less than the 3rd percentile. Heat wave caused an increase in cardiovascular

morbidity by 8% (95% CI: 5, 11) and the cold spell increased hospital admissions by 33% (95%CI: 28, 37).

Discussion

We presented the association between extreme temperatures and CVD mortality and morbidity, through studies conducted in LMICs, in an attempt to illustrate the situation during the last ten years. To our knowledge, there are only a few reviews focusing on LMICs in this context. Until now, most research was directed towards climate change and infectious diseases, rather than NCDs. Moreover, most studies focus on all-cause mortality, rather than CVD mortality.

One limitation to our research was that many of the included studies had inconsistent results. This problem derives from many causes. At first, since there are no standard technical terms, different definitions for cold and heat were used in almost every study. Moreover, the threshold temperature, as well as the duration and the intensity of the extreme phenomenon, vary among the studies. These inconsistencies prohibit the generalization of the results. However, we can identify some common patterns. In general, temperature- mortality curves are U-shaped, implying that mortality is typically lower in mild temperatures and it increases at more extreme ones. Another commonly shared observation was that the effect of high temperatures was more immediate, but the effect of low temperatures lasted longer. Finally, we observed that the dose-response curve was steeper in the beginning. This observation could be attributed to harvesting mortality. However, regarding this matter, there is no clear consensus. Some researchers support that all deaths at the beginning of a heat waves are contributed to harvesting mortality, while others found no mortality displacement (85). It is possible that the wide variation between studies is due to different preparedness of public health systems, among different countries. Also, the intensity and the duration of the heat wave, could affect the phenomenon of mortality displacement.

Additionally, it is important to highlight the fact that in most of the studies, we observed the influencing role of latitude and populations' ability to adapt to local climate. Populations in tropical and sub-tropical climates were found to be more vulnerable to low temperatures, but more resilient to extremely high temperatures. For southern countries of the boreal hemisphere, the U-shaped curve shifts to the right, because threshold temperatures are higher, than in the northern countries. This fact implies that the effect of

acclimatization needs to be taken into consideration, when evaluating the effect of climatic conditions. Moreover, most studies have found higher mortality and morbidity risks for the elderly. One possible explanation could be the fact that the thermoregulatory system deteriorates with age, aged people are more frail, due to pre-existing medical conditions and at the same time this population is more likely to live alone (86).

Discussion, Limitations and Future Research

There are several limitations to the included studies and the results must be interpreted with caution, mostly due to the lack of control for possible confounding factors. Most researches present the association of temperature with CVD, without taking into consideration variables, which are proven to be related to CVD mortality and morbidity, such as the air pollution levels in the studied region. Only one study controlled for air pollutant levels and humidity (73). This limitation poses a great problem to the interpretation of the results, because it is probable that there is a cumulative effect of temperature and air pollution on cardiovascular health (4). Other potential confounding factors include the seasonal Influenza, preexisting medical conditions, occupation and daily life habits, such as smoking status, exercise or even potential homelessness. All of the above, could affect the amount of time spent outdoors and therefore, increase the duration of the exposure to extreme temperatures.

There are also other modifying factors, which were not thoroughly analyzed in current literature, such as sex, comorbidities, and educational status. For instance, in some of the studies, males were found to be more vulnerable to temperature changes than women (79), while other studies support the opposite association (80). Furthermore, since our studied variables are mortality and morbidity, we should also control for potential comorbidities, as well as for the general health status of the studied population. For example, Tibetan men have been found to be less healthy than women and this fact could affect the interpretation of the final results (79). A great limitation is that it is not safe to generalize the collected results, as only a few of existing studies provide statistically significant results.

Future research should focus on the combination of multicity, times-series analysis and ecological studies, in the purpose of clarifying the role of potential modifying factors and being able to provide safe results on CVD mortality and morbidity. Local climate and acclimatization are undeniable factors, which affect temperature’s impact on CVD mortality

and morbidity. Therefore, they should be taken into consideration and evaluated in a systematic way. There is also great need for an agreement on common technical definitions, in order to comprehend the precise association between climatic conditions and human health. Common terminology is also needed, to draw universal strategies of prevention and control. Finally, it is urgent to encourage more research on the African continent, as it is estimated to be profoundly affected by climate change, but stands helpless because of structural inefficiencies.

Chemical Pollution and Cardiovascular Disease

Mesoamerican Nephropathy

In bibliography, the term “Cardiovascular Disease” entails Ischemic Heart Disease and Stroke. Both, are clinical manifestations of underlying angiopathy, among other causes. For the purposes of this essay and in order to enlighten an important, yet poorly addressed Public Health issue in LMICs, we will elaborate on a medical condition, known as “Mesoamerican Nephropathy” (MeN). Similarly to Stroke and IHD, MeN could be associated to a disorder of blood perfusion in the arterial vascular system, even though the exact pathophysiology remains unclear. The term “Mesoamerican” derives from the geographical distribution of the disease. It is also known as “Kidney Disease of Unknown Etiology” (CKDu), because even though it involves findings of elevated creatinine and proteinuria, it is not attributable to conventional risk factors, such as hypertension, diabetes mellitus etc. (87). The clinical image of the disease consists of asymptomatic elevation in serum creatinine, while some subjects complain of dysuria. Blood pressure can be slightly high (88). Gradually, MeN leads to end stage renal failure, which is the cause of death among the patients. The available data show that in some LMICs, more specifically in El Salvador and Nicaragua, the disease constitutes the most common cause of premature death among young adult males (89).

Mesoamerican Nephropathy affects unevenly the LMICs and more particularly, subgroups of populations exposed to high temperatures. The prevalence of MeN is high in rural, agricultural regions, but also in communities involved in activities, such as mining and fishing. All these regions share one common characteristic, which is high temperatures and humidity (89). The disease is most common among adult, male, agricultural workers, mostly sugarcane workers in Central America and more particularly, in Nicaragua, Costa Rica and Ecuador (90). There are also other “hotspots” of CKDu in Sri Lanka and India. In these regions, sugarcane workers are expected to work up to 12 hours a day, in temperatures that range from 34°C to 42°C (91). In El Salvador, chronic renal failure is unexpectedly high among adult farmers too, with a prevalence of 12.7% (92). It is also the country with the highest mortality rate from kidney disease in the world (91).

The common histological characteristic of most cases is the tubulointerstitial nephritis (93). However, the pathophysiology of the disease is not clarified. There are three suggested pathways in literature. The first major causative pathway involves recurrent episodes of dehydration, repeated heat stress and loss of potassium and sodium from the kidney. A hard working person might lose more than 5 liters of sweat per shift. Since access to clear water in such working places is not always a given, recurrent dehydration causes diminished renal perfusion and glomerular ischemia. Repeated episodes through the years, cause continuous damage to the tissue, increase localized inflammation and finally lead to fibrosis and renal impairment (89). Added to this process, subclinical rhabdomyolysis, due to harsh work, causes additional damage to the kidney. Finally, the "fructokinase induced pathway" is suggested to aggravate the renal damage. More specifically, workers' habit to use drinks with high fructose and sugar in order to rehydrate, seems to increase the nephrotoxic effect of heat stress (91).

Another possible pathway involves the long term exposure to chemicals and pesticides (94). Many categories of agrochemicals, banned in developed countries, are still in use in LMICs. Among them, there are many, which are blamed to have a potential nephrotoxic impact, such as silica. However, no specific substance has been identified as accountable for CKDu until now (95). Moreover, the theory of exposure to chemicals fails to explain the prevalence of the disease in other groups, such as miners and fishers. Finally, infectious agents, such as Leptospira and hantavirus could be also associated to the disease (89). What is most probable though, is that all the above factors have a cumulative impact to the kidney, with the heat-induced angiopathy having a predominant role in renal damage.

Defining the exact prevalence of MeN is challenging. Many of the countries, where the entity is present, do not have formal patient registries or adequate epidemiological systems of surveillance. Thus, there are only limited publications from LMICs and the extent of the burden, imposed by this disease, is unknown. In a study in Nicaragua, 29 sugarcane cutters with no existing nephropathy, were included in a longitudinal study, which aimed to reveal an association between working in extreme temperatures and renal function impairment. 25 non- sugarcane cutters where used as control group. Pre-shift and after-shift renal function were examined for 9 weeks. At the end of the study period, there was a 16% ($p=0.002$) increase in mean serum creatinine and the mean GFR had decreased by 10ml/min ($p=0.02$) (88). In the same context, sugarcane workers, with no pre-existing renal conditions, were compared to a control group. The control group included people, whose

occupations did not demand long hours of work in extreme heat. Sugarcane workers were examined before harvesting period and they were followed up in 6 and 12 months. Working as a cane worker, was related to a 20% (95%CI: 13, 27) higher creatinine level at the end of the study period (96).

Mesoamerican Nephropathy constitutes an epidemic, not only in Central America, but also in other regions of the world, all exposed to extreme heat and humidity. Thus, some researchers consider MeN to be a direct outcome of global warming and recommend the term “heat stress nephropathy” to define it (95). Even though research in this field is limited, it is evident that the disease affects, disproportionally, young adults, in marginalized and poor communities in LMICs. Therefore, it is urgent to address the problem and mitigate it through prevention and control policies.

Pesticides, Agrochemicals and Cardiovascular Disease

Agrochemicals and pesticides are widely used in the world. Food insecurity in LMICs, due to political instability, wars and climate change, increase their necessity. Only in the database of the European Chemicals Agency, there are more than 150.000 different substances registered, yet only 20% of them have been properly evaluated for their risks on human health (97). In many of the LMICs, economy is often based on agriculture, but the legislation on the use of chemicals, is still underdeveloped. As a result, thousands of people, mostly in agricultural regions, are exposed to agrochemicals, never tested for toxicity. Current literature provides information on the effect of chemicals on the nervous and blood system, as well as their impact on carcinogenesis. However, limited research has been conducted regarding their association with Cardiovascular Disease (98). The National Health and Nutrition Examination Survey (NHANES) is one of the few national studies, showing a positive association between the concentration of pesticides and CVD, among farmworkers in USA (99). However, national studies from LMICs do not exist.

The use of Organophosphates (OPs) is an important public health issue in LMICs, because OPs are widely used for the control of agricultural and industrial pests. The basic mechanism of their toxicity involves the inhibition of the acetyl-cholinesterase (AChE) enzyme. Acetylcholine’s accumulation in the autonomic system causes alterations to the circulatory system and damages the cardiac tissue. In a retrospective cohort study in Taiwan, poisoning by OPs was associated to a rise of cardiac arrhythmias and coronary disease. The risk of arrhythmia and coronary disease was higher among the OPs exposed

group, with an OR= 1.25 (95%CI: 1.07, 1.39) and OR= 1.13 (95%CI: 1.01, 1.27) respectively (100).

Discussion

Chemical pollution is an emerging threat for human health in a global level. Concentrations of substances produced by industrial procedures, agrochemicals and pesticides increase. People are exposed to these chemicals in many ways and more often, through agriculture, consumption of fruit and vegetables or drinking water from polluted sources. Nevertheless, research on the long term effects of such exposures on human health is limited, especially in LMICs. More particularly, the association of chemicals with CVD is unclear, even though there is emerging literature from studies conducted in HICs, suggesting that there is a strong causal relation.

Future research should focus on the association of widely used chemicals with CVD. It is an essential need to address this matter through the conduction of national studies. Moreover, we should underline the fact than race, ethnicity, poverty and low socioeconomic status are related to higher levels of exposure to environmental pollutants (101). Therefore, it is also important to address the social determinants of health in this context. Finally, we should raise awareness in relation to micro plastics. Micro plastics enter the ecosystems from a variety of sources, such as clothes, cosmetics, and industrial processes. Nevertheless, because of the absence of population-wide studies, their impact on human health is uncertain (102). Overall, chemical pollution's impact on CVD is underestimated and future research should focus on ways to uncover this impact and find ways to mitigate it.

Overall Discussion

Key Findings, Limitations and Strengths of the Study

By conducting this review, we found evidence suggesting that air pollution, climate change and chemical pollution constitute substantial risk factors of CVD in LMICs. More specifically, we found that for a PM increase of 10μg/m^3, CVD mortality and morbidity increases, ranged from 0.25% to 1.22% and 0.14% to 0.26%, respectively. Stroke mortality and morbidity ranged from 1.22% to 3.43% and 1.16% to 1.37%, respectively. The results are in accordance with multicity studies conducted in HICs, such as the APHENA study (103). We must underline again that the concentration of air pollutants is much higher in LMICs, therefore the overall effect of these factors on CVD mortality, could be is higher in LMICs. As for climate change, increases of temperature resulted to an increase from 1% to 7% for CVD mortality in many LMICs, as described before. Respectively, increased temperatures in Europe were associated to an increase of CVD by 1.84% to 3.2% (85). Moreover, we found evidence, supporting that the combination of high temperatures and use of chemicals, increase the incidence of CVD in some regions of the world, such as countries of Central America. Finally, we found that exposure to pesticides and chemicals could be related to an OR from 1.13 to 1.25 for cardiovascular events.

Our study has several limitations. Firstly, different local climatic conditions, different technical definitions of hot and cold, as well as different PM distribution models and populations' characteristics, all together, forbid the generalization of the selected data. Among the studies, there was heterogeneity between population samples, methodologies and use of confounding factors. Therefore, despite the fact that their results do not differ a lot, further investigation is needed. Moreover, the fact that Public Health in LMICs lacks preparedness, could affect the impact of extreme conditions, such as heat waves, on the community. Moreover, environmental conditions could cause higher mortality rates in LMICs, compared to HICs, due to their less developed health systems. Finally, some of the most vulnerable regions, such as Sub-Saharan Africa, are poorly represented in literature, even though 32% of Africans are exposed to pollution levels higher than WHO standards (55).

To our knowledge, this is the first study which focuses on the association of CVD with all three environmental factors. We managed to elucidate an under-investigated Public Health issue in LMICs, through a thorough and detailed review of the existing literature, of

the last 10 years. We included studies, which complied with strict selection criteria and provided detailed information on their methodology and results. We also revealed some important, yet poorly addressed confounding factors, which could affect substantially the effect of the environment on the cardiovascular system. This is the first study which illustrates the role of these factors as a whole, contributing to the creation of a more solid background for the design of future studies. Overall, even though our study does not provide concrete numeric results, we managed to raise awareness about a critical issue in LMICs, while providing a useful theoretical feedback for future research.

Suggestions for Future Research

Throughout the three main chapters of this essay, we suggested fields of future research, in a technical and detailed way, independently for each one of the three environmental factors. Now, we will present a broader spectrum of existing needs and gaps and we will suggest ways to fulfill them.

Evidence from LMICs is limited. Most studies are conducted in China and fewer in Latin America and India. In general, there is need for national, prospective studies, in order to reveal the exact association of CVD with the concentrations of the various pollutants, the duration of exposure to them and with short and long-term exposure to different temperature ranges. Moreover, most of the existing studies on air pollution and climate change, examine these variables separately. However, there is adequate evidence suggesting that in fact, these factors have a cumulative effect, not quantifiable for the moment. As a result, future research should focus on the use of multi-variable models, which examine both factors at the same time and in a prospective way.

Furthermore, since there are different exposure profiles, such as PM size distribution and composition, different regional climate, population characteristics and acclimatization, future research should have as a goal to enlighten these different patterns among countries. Additionally, social determinants of health, such as educational and economic status should also be investigated in this context, as it is unclear if and to what extent, these factors are effect modifiers. Insights into the factors mentioned above, could create different guidelines for different places of the world.

Between 2000 and 2016 the number of people exposed to extreme heat increased by 125 million. Evidence from a variety of climate models shows that Earth's temperature could increase from 1.1° C to 5.4° C by 2100 and that this increase depends completely on

the energy choices that the humanity will make in the next years (104). At the same time, air pollution constitutes a major Public Health issue, globally. WHO suggests specific guidelines for the concentration of the various air pollutants. More specifically, the guidelines suggest that the annual and daily, mean concentration for $PM_{2.5}$ is below 10μg/m^3 and 25μg/m^3 respectively, while the maximum concentration for Ozone should be below 100μg/m^3 every 8 hours. According to the 2016 Urban Air Quality database, 98% of urban areas with more than 10.000 habitants in LMICs, are exposed to concentrations of air pollutants, which are higher than the WHO guidelines (33). Furthermore, chemical pollution could be a potential, novel risk factor of CVD. It has an unclear impact on mortality and morbidity, but evidence shows that it affects the cardiovascular system in a negative way.

All these environmental factors cause an accelerating increase of the incidence of CVD in LMICs. Thus, the Paris Agreement is clearly one of the most important health agreements of the century. On top of this effort, a new global strategy on health was approved at the 72th Annual World Health Assembly in 2019, which outlines the transformation needed in order to improve health and well-being through climate action (105). In this context, ambitious mitigation initiatives are necessary, in order to decrease air pollution levels worldwide and limit warming to 1.5°C, while trying to achieve sustainable development (106).

Conclusions

The association between the environment and CVD, proves that human behavior and lifestyle alone, fail to explain the whole spectrum of the disease. On the contrary, there is an urging need for the states to claim their responsibilities, which among others, is to maintain and promote the health of their citizens, by contributing to the creation of healthy environments. To achieve this goal, states should take action towards the development of sustainable urban planning, adoption of strict environmental legislation and compliance with world standards of environmental health. Applying CVD prevention programs, which target only the four conventional risk factors, meaning tobacco, unhealthy diet, alcohol and physical exercise, is ineffective. If others, equally important drivers exist, but are not addressed, no long-term improvement will be achieved. Therefore, it is an indispensable necessity to face the physical environment as an undeniable determinant of health and to address it equally to other, conventional determinants, such as behavior, biology and social influence.

The negative health impacts of environmental factors are largely preventable with specific health actions (105). Multiple sectors must be urged to shoulder their share of responsibility and get involved in the process of tackling CVD in LMICs, but also globally. Sectors beyond the health sector, such as energy and transportation sector, should be implicated in action. Solutions on energy saving, and reducing of emissions, alternative sources of energy and investments on eco-friendly technology should be encouraged, towards the desired balance between the technological evolution and the preservation of the populations' health status. At the same time, it is critical to embody equity issues into global policies. Environmental threats are concentrated in the less developed countries of the world, even though in most cases, these are the regions that contribute least to pollution and climate change. Overall, mitigating the effect of the environmental factors, is highly complicated and demand an action plan, deriving from multisectoral cooperation, enforcing the concept of "Health in All Policies" (107).

In this concept, the role of prevention and health promotion should be enhanced and expanded. At the moment, prevention campaigns and guidelines are vertical. All countries

are expected to adopt similar targets and implement similar health policies, despite of the underlying economic gaps and the wide developmental and cultural differences among them. Little attention has been paid to understanding what LMICs can do differently, so that personalized, cost- effective preventive strategies, are implemented and adapted to different country-profiles and needs. Overall, it is critical to incorporate more population-based prevention programs to the health promotion agenda, because CVD, as most NCDs, has not been properly addressed in LMICs (12). At the moment, there is no global health institution dedicated to NCDs and there is no public donor with an agenda on tackling CVD in LMICs. Even though NCDs are accountable for the majority of deaths worldwide, they receive only 2% of the global health funding, leaving poor countries to confront the problem alone (4).

Current prevention strategies should be replaced with sustainable targets, which comply with ecosystem function, in order to include the ecological aspect of health in policy making. An ecological approach needs to be incorporated in our scientific methods, when addressing CVD as a Public Health issue. Such an approach, contributes to the understanding of the interactions between biological, social, cultural and material dimensions of health and therefore, favors a holistic, multidimensional approach in line with the concept of “Planetary Health”.

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Charts

Chart 1

Percent increase (and 95%CIs) of mortality associated with 10μg/m³ increase in air pollutants' concentrations.

Cause of mortality	TSP		SO_2		NO_x	
	Basic model[a]	Adjusted model[b]	Basic model[a]	Adjusted model[b]	Basic model[a]	Adjusted model[b]
All-cause	0.2 (−0.1, 0.5)	0.3 (−0.1, 0.6)	1.8 (1.4, 2.2)*	1.8 (1.3, 2.3)*	1.2 (0.2, 2.2)*	1.5 (0.4, 2.5)*
Cardiovascular	1.3 (0.7, 0.8)*	0.9 (0.3, 1.5)*	4.8 (4.0, 5.6)*	3.2 (2.3, 4.0)*	2.7 (1.0, 4.3)*	2.3 (0.6, 4.1)*
Respiratory	−0.1 (−1.1, 0.9)	0.3 (−0.6, 1.3)	1.5 (0.3, 2.8)*	3.2 (1.8, 4.7)*	1.7 (−1.3, 4.8)	2.6 (−0.2, 5.6)
Lung cancer	0.6 (−0.6, 1.7)	1.1 (−0.1, 2.3)	4.0 (2.4, 5.6)*	4.2 (2.3, 6.2)*	1.6 (−2.0, 5.3)	2.7 (−0.9, 6.5)

[a] Covariates included age and sex.
[b] Covariates included age, sex, BMI, physical activity, education, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension.
* $p < 0.05$.

Chart 1: Percent increase of mortality associated with 10mg/m³ in air pollutants (46)

Chart 2

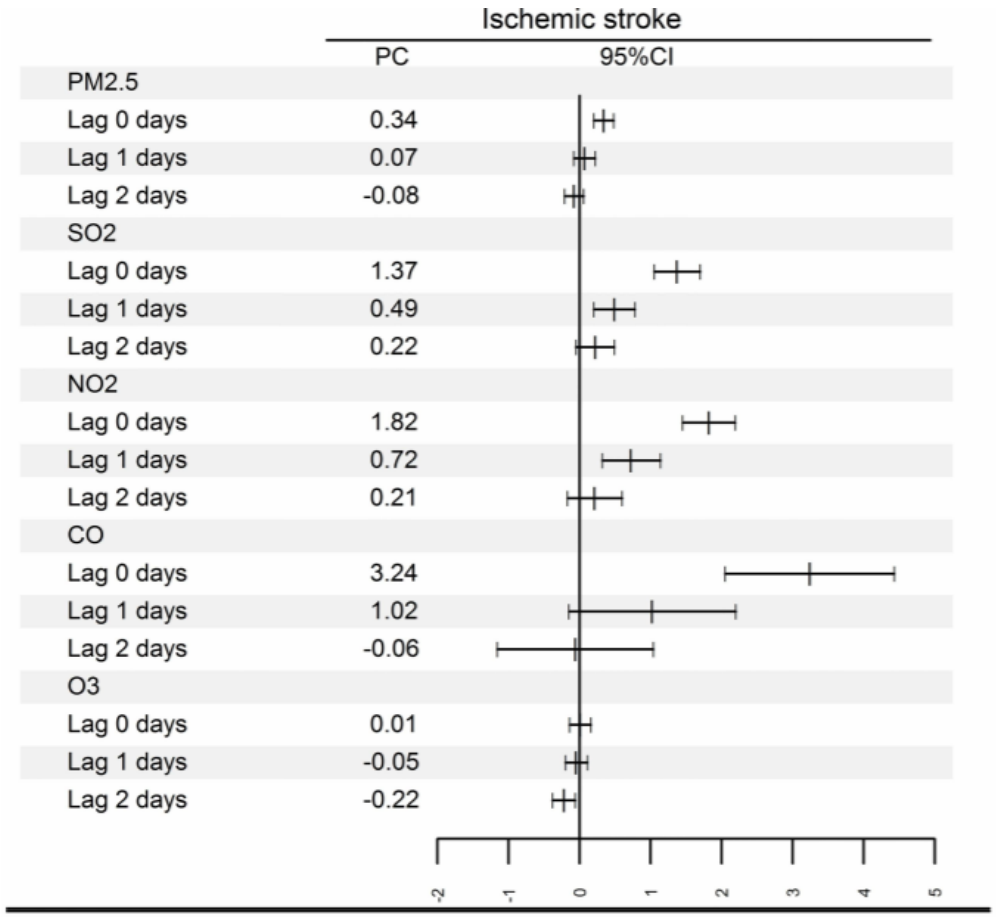


Fig 2. PC and 95% CI in daily hospital admissions for ischemic stroke associated with increases of 10 μg/m³ in $PM_{2.5}$, SO_2, NO_2, and O_3 and 1 mg/m³ in CO concentrations at different lag days. CI, confidence interval; PC, percentage change.

Chart 2: PC and 95%CI in daily hospital admissions for stroke with increases of 10mg/m3 in $PM_{2.5}$, $S0_2$ NO_2, O_3 in different lag days

Chart 3

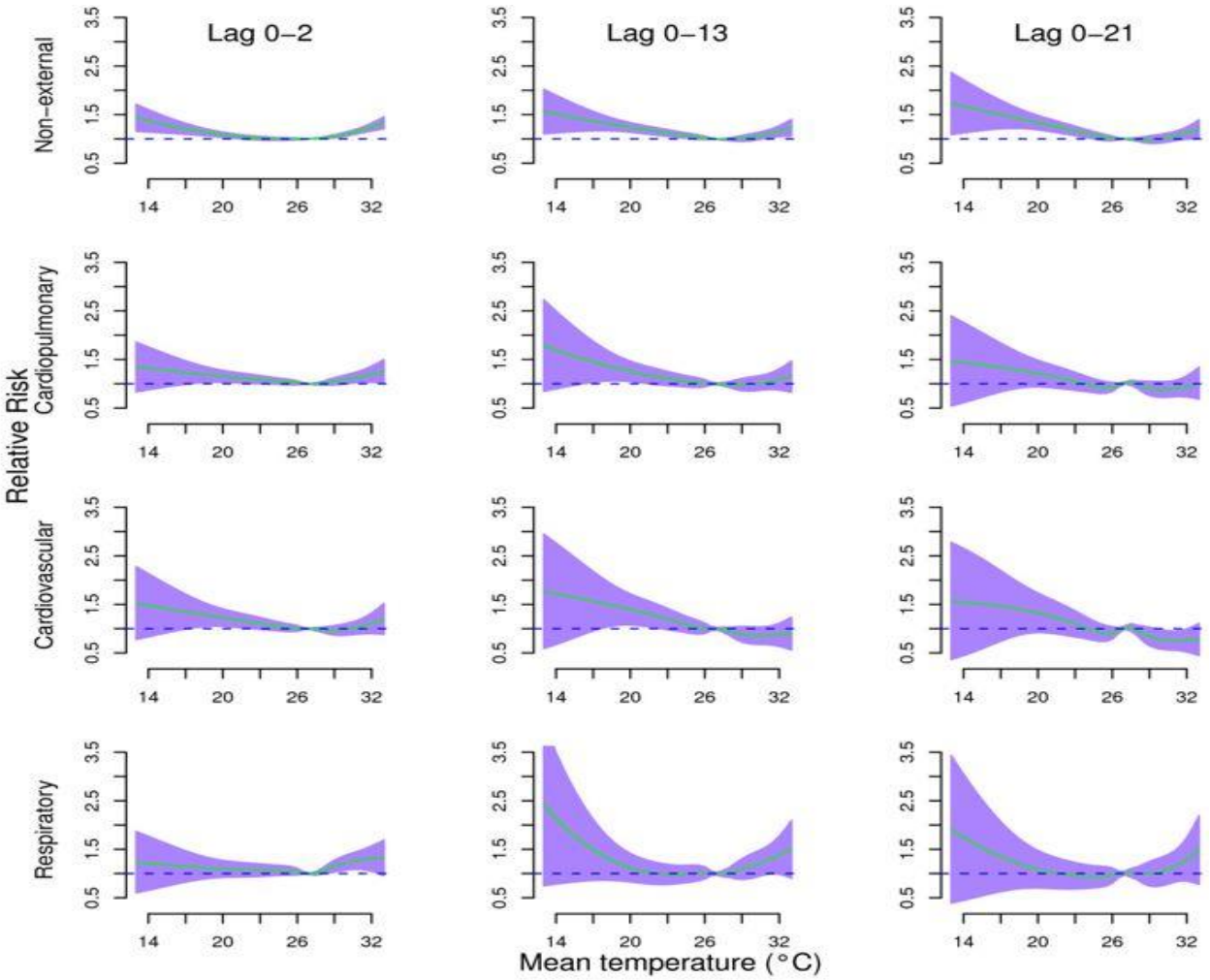
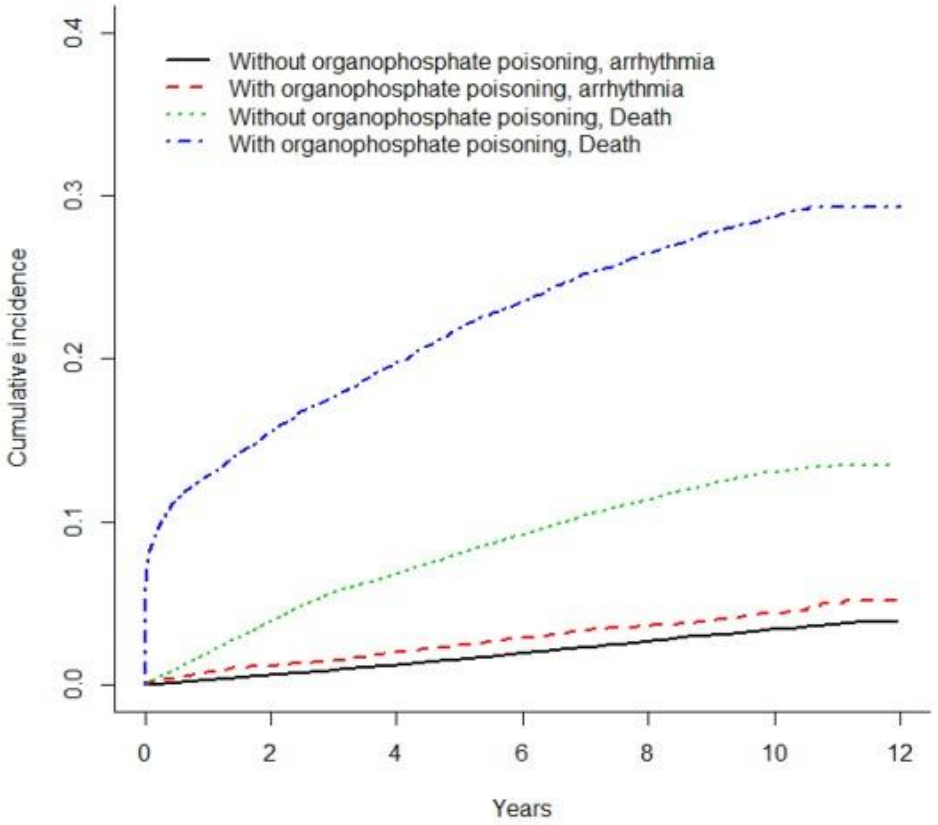


Chart 3: Temperature's impact on cardiovascular mortality was studied for lags 0-2, 0-13 and 0-21 (73)

Chart 4



OPs poisoning, No.							
At risk	7561	5739	4795	3743	2608	1255	0
Arrhythmia events	0	87	139	189	222	243	253
Non-OPs poisoning, No.							
At risk	30244	26435	22627	18138	12819	6394	0
Arrhythmia events	0	174	335	501	627	714	734

Chart 4: The association of exposure to OPs with incidence of cardiovascular events (100)