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Review article

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Skin-interfaced wireless biosensors for perinatal and paediatric health

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Abstract

Continuous monitoring of the parameters that define physiological health status is an essential aspect of modern care for critically ill patients, particularly for vulnerable populations. Current hospital-grade systems for such purposes involve sensors taped to the skin, with hard-wired connections to large, expensive data-acquisition and display systems. Soft, wireless, skin-interfaced alternatives reduce associated burdens on the patients, simplify operations in clinical care, minimize risks of adhesive-induced skin injuries and reduce the costs of monitoring, as recently demonstrated in devices designed for maternal, foetal and paediatric health. The implications extend beyond hospital and home settings in well resourced areas of the globe to remote clinics in low and middle-income countries. This Review summarizes the latest progress in this research area, with an emphasis on the growing range of options in device configurations and form factors, sensor modalities and operational features. Examples of technologies capable of monitoring all key vital signs as well as various unconventional metrics of health status highlight the transition from academic prototypes to manufactured systems and scaled deployments.

Sections

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Key points

- Continuous physiological monitoring is an essential aspect of modern healthcare for the critically ill, especially perinatal and paediatric patients.
- Wireless monitoring technologies reduce patient discomfort, risk of iatrogenic injury and healthcare provider burden while informing and guiding many aspects of clinical care.
- Soft, compliant, miniaturized skin-interfaced sensors enable safe and reliable connectivity to the skin of the most fragile patients at different body locations, without straps, bands or abrasive adhesives.
- Cost-effective engineering designs and manufacturing techniques allow for the practical use of advanced technologies in low-resource settings.
- Broad, multi-modal data streams collected in healthcare facilities or in home settings can serve as the basis for a data-centric approach for early intervention and patient care.

Introduction

Maternal, foetal and paediatric health are key priorities for the United Nation's 2030 Sustainable Development Goals in the area of health and well-being. Unfortunately, halfway through this 15-year global effort, little progress has been made in reducing maternal and neonatal mortality worldwide[1]. More than 200 million women experience pregnancy annually and approximately 140 million babies are born every year, globally[2,3]. Mortality rates remain, however, unacceptably high; 23.8 maternal deaths occur for every 100,000 births in the USA. This number rises to 462 maternal deaths per 100,000 births in low and middle-income countries (LMICs)[4]. Approximately 295,000 women die because of pregnancy-related complications yearly, and 94% of these deaths occur in LMICs[5]. Complications in childbirth inevitably affect newborns. The average mortality for neonates is 34 deaths per 10,000 live births in the USA; regionally, neonatal mortality is highest in sub-Saharan Africa and South Asia, where rates are 270 and 240 neonatal deaths per 10,000 live births, respectively[6]. As with maternal deaths, marked disparities exist across regions and countries. Regrettably, many of these deaths and other adverse outcomes are avoidable through improved access to quality health care, especially in LMICs, where economic considerations impose severe constraints on the availability of supporting technologies. The health of a foetus and neonate affects their well-being early in their childhood, with lasting effects that persist at each stage of development through to adulthood. Moreover, negative and positive effects compound over an individual's lifetime and throughout communities[7]; shortcomings in antepartum, neonatal and paediatric care directly translate into poor life quality at all subsequent ages, with dramatic consequences for the ability to contribute as a productive member of society. Treating health conditions in adulthood is almost always more expensive and difficult than it is to make preventive efforts during paediatric life. These considerations highlight the importance of maternal, foetal and paediatric care as top priorities for any society.

For these uniquely vulnerable and fragile patients, healthcare monitoring often occurs in controlled hospital settings such as neonatal and paediatric intensive care units (NICUs and PICUs) or childbirth facilities. The current standard involves a collection of rigid and/or bulky sensors that adhere to the skin or penetrate it, where hard-wired connections serve as interfaces to large, expensive data acquisition and display systems. These systems have changed minimally over the past 30 years, in part because commercial interest has been limited by smaller addressable market sizes compared to those associated with technologies that target broader populations or widespread conditions such as heart disease, for example[8]. This neglect has negatively affected the well-being, cost and quality of care, and the final health outcomes of patients in need. The limitations of existing monitoring systems include iatrogenic injuries caused by strong adhesives between the sensors and the skin[9–11], physical constraints on natural movements, and complications imposed on even the most basic aspects of patient support such as changing napkins (diapers) and therapeutic holding and skin-to-skin contact by parents and care-givers. Although these disadvantages mainly affect paediatric patients when monitoring foetal heart rate (FHR), maternal health and uterine contractions during labour suffer from similar engineering drawbacks, such as those found in rigid tocodynamometer systems that affix to the abdomen with straps and wires that tether the patient to a wall-mounted base unit (Fig. 1a). As with NICU and PICU facilities, these operations also require controlled facilities and direct supervision by trained clinicians and support staff, thereby adding to care complexity and costs, and preventing widespread use in LMICs, where need is greatest.

Scalable development of soft, miniaturized wireless electronic sensors that gently and safely integrate with the skin at relevant anatomical locations to form body area networks has the potential to enable continuous, clinical-grade measurements of traditional vital signs along with other important signs of health and well-being[12,13] (Fig. 1b). Furthermore, these systems can be connected to cloud computing infrastructures, thereby supporting clinical decision-making with artificial intelligence and machine learning algorithms. This Review summarizes recent advances in the area of wireless, wearable biosensor technology, with an emphasis on systems with proven utility throughout the intrapartum period, and in neonatal and paediatric care across dedicated facilities and home settings. The scope encompasses not only traditional monitoring parameters, but also unconventional metrics of health status. The content spans advanced commercial systems as well as mature research devices tested on a meaningful number of patients that establish operational effectiveness for scaling up in future. The descriptions also highlight opportunities and existing deployments in LMICs through philanthropic support.

Physiological markers of health status

We introduce the main health risks and the monitoring needs of each class of vulnerable patient population, including perinatal (maternal–foetal) and paediatric (neonates, infant and child) (Fig. 2).

Maternal and foetal health

Various complications can occur during pregnancy, labour, delivery and the postpartum period, including hypertensive disorders, infection, sepsis, thromboembolic events and maternal haemorrhage, each with associated risks of morbidity and mortality[14–18]. Moreover, pregnancy occurs within the context of pre-existing health conditions; as societal trends of delayed childbearing continue, pregnant patients will be older with more baseline comorbidities that increase the risks of pregnancy[19]. A nationwide cross-sectional study in the USA found that 60% of all pregnant patients in 2019 had at least one pre-pregnancy

cardiovascular risk factor (hypertension, diabetes or obesity)[20]. Maternal comorbidities and pregnancy-related complications incur risk to the foetus because they can interfere with the establishment of the pregnancy, implantation and the subsequent supply of nutrients and oxygen essential for the growth and maintenance of the foetus. The consequences can present themselves as congenital birth defects

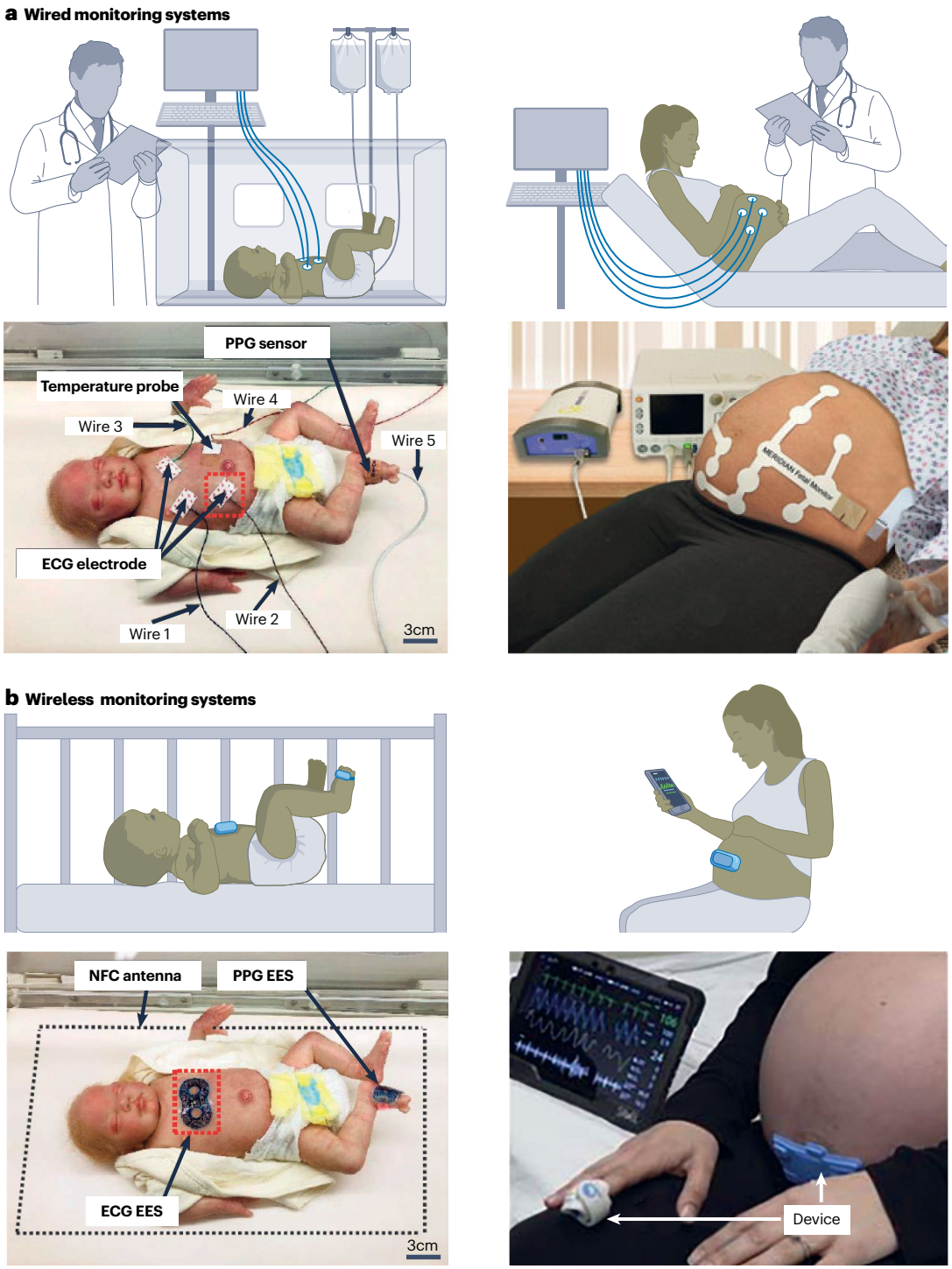


Fig. 1 | Comparisons of traditional and emerging monitoring technologies for maternal and paediatric health. a, Illustrations and images of wired monitoring systems for paediatric patients and pregnant women. PPG, photoplethysmography. **b**, Illustrations and images of corresponding wireless monitoring systems. NFC, near-field communication; ECG, electrocardiogram; EES, epidermal electronic system. Parts **a** and **b** (bottom left) are reprinted with permission from ref. 72, American Association for the Advancement of Science. Part **a** (bottom right), image courtesy of Mindchild Medical, Inc.

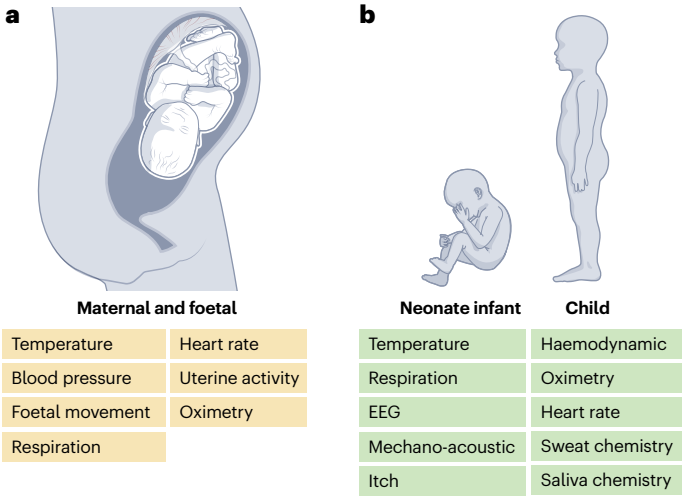


Fig. 2 | Diagrams of physiological markers of health status from different patients. a, An overview of seven physiological markers for maternal and foetal health: temperature, blood pressure, body sounds (foetal movement), respiration, heart rate, uterine activity and oximetry. **b**, Overview of ten physiological markers for paediatric health: temperature, respiration, electroencephalogram (EEG), body sounds, itch, haemodynamics, oximetry, heart rate, sweat chemistry and saliva chemistry.

(compatible or incompatible with life), intrauterine growth restriction, stillbirth or premature birth[21–23]. Fortunately, complications of pregnancy and delivery can often be anticipated by detecting evolving abnormalities in maternal and/or foetal vital signs. Thus, accurate, continuous monitoring of physiological biomarkers is essential to prompt maternal–foetal predictive assessments and early interventions to reduce morbidity and mortality[14–16,24].

The most common parameters measured during the antepartum and intrapartum period are maternal vital signs (heart rate (HR), blood pressure (BP), respiratory rate (RR) and temperature), uterine contractions and FHR[25–29]. Ensuring accurate and continuous measurement of uterine contractions and FHR requires careful placement of the sensors, regular adjustments to account for maternal and foetal movements, robust interfaces with the skin and removal of motion-related artefacts accompanying labour and childbirth[30–34]. Insufficient quantity and/or quality of information can frustrate and compromise clinical decision making[35–38]. Monitoring additional vital signs (such as RR, temperature or BP) non-invasively from the mother is often necessary both intrapartum and following delivery. Immediately after delivery, with its dramatic fluid loss, is a uniquely vulnerable time for pregnant patients, particularly after complicated vaginal or Caesarean deliveries. Measurements of maternal vital signs during labour are most often not continuous, and each collection of a set of vital signs requires skilled clinical staff and multiple devices to obtain all relevant clinical biomarkers[39].

In addition to routine biomarkers, technological advances allow for detection of other physiological measurements such as foetal movements by ultrasonographic evaluation and maternal report, which can inform not only clinicians but also the mother[40–42]. Likewise, continuous monitoring of maternal BP can detect hypertensive disorders of pregnancy including preeclampsia, thereby enabling prompt medical evaluation. Tracking of core maternal body temperature can reveal the development of infection, as well as inadequate peripheral perfusion and volume status caused by blood loss in obstetric emergencies[39,43–45]. Although not yet routine in clinical practice, non-invasive monitoring of foetal pulse oximetry can enable early detection of foetal hypoxic distress[46].

Paediatric health

Paediatric (from birth through age 21 years) health includes neonates (birth to 28 days), infants (29 days to 2 years old), children (2 years to 12 years), and adolescents (12 through 21 years)[47]. This Review primarily focuses on the neonate, infant and child subpopulations.

As with adults, paediatric patients can suffer from various health conditions, but dramatic differences in anatomy, physiology and developmental status lead to unique challenges in monitoring and provision of care. For example, the heads of neonates and infants are disproportionately larger than the rest of their bodies compared to adults, which increases the risk of airway obstruction with neck flexion[48–51]. Specifically, the geometry of the paediatric airway, which is smaller in diameter and length, and the relatively larger size of the tongue in the hypopharynx, predispose neonates to compromised airways[48,51]. Physiological differences are also apparent; the total blood volume in paediatric patients (70–90 ml kg^{-1}) is lower, whereas oxygen usage (6 ml kg^{-1} min^{-1}) and CO_2 production (100–150 ml kg^{-1} min^{-1}) are higher[48,51] compared to adults (blood volume 65–70 ml^{-1} kg^{-1}, oxygen usage rate 3 ml kg^{-1} min^{-1}, CO_2 production rate 60 ml kg^{-1} min^{-1}). Therefore, with respect to body weight, for tidal volumes similar to those of adults, paediatric patients require a faster RR to compensate and remove CO_2 (refs. 48,52). Moreover, the normal range of BP, RR and intracranial pressure vary at different ages, resulting in variable thresholds for tachycardia, tachypnea and hypo/hypertension[51,53,54]. These considerations have important implications for paediatric patients undergoing surgical procedures with airway control during intubation, and for precise control over intraoperative BP to maintain healthy levels of perfusion while reducing the risk of bleeding. The collective consequence of these considerations is an increased level of vulnerability associated with this population[55,56].

The standard of care in the PICU and NICU consists of multiple 'paediatric-sized' medical equipment (invasive and non-invasive) to enable continuous monitoring and treatment of the patient, including: catheters/lines (for example, peripheral and central venous catheters to measure peripheral venous pressure and central venous pressure, respectively, arterial catheters to measure BP, nasal cannulas/capnographs to measure end-tidal CO_2, oxygen masks for oxygen therapy, ventricular catheters to measure intracranial pressure); mechanical ventilators (a tracheotomy/endotracheal tube delivers oxygen and removes CO_2); and wired monitors (adhesive electrodes to measure HR/RR, pulse oximeters to measure pulse rate and blood oxygen saturation (SpO_2), BP cuffs)[57–59]. In many cases, neural and neuromuscular electrical activity must also be measured using electroencephalogram (EEG) and electromyogram data, respectively[60,61], for diagnosis of disorders such as epilepsy, muscular dystrophy and neuropathy[62]. Unfortunately, owing to several factors including more limited commercial market opportunities, many paediatric devices are not United States Food and Drug Administration (FDA)-cleared and are used off-label from adult systems.

Within paediatric populations, neonates are an especially challenging subset because of the wide spectrum of essential physiological milestones they must achieve within a narrow timeframe. Neonatal health encompasses the complex and disparate needs of healthy and

critically ill premature, postmature and full-term babies from birth to the first 28 days of life[63]. For example, the 60 seconds following complete delivery of an infant from the pregnant patient have been named 'The Golden Minute'[64]. During this timeframe, infants transition from the intrauterine to extrauterine environment and must begin to breathe, cry and self-regulate their temperature. If a neonate fails to transition independently, nearly instantaneous monitoring of vital signs such as HR, RR and pulse oxygenation is essential to guide healthcare providers in prompt resuscitation. Failure to act during this 'Golden Minute' can lead to immediate hypoxia and long-term neurodevelopmental injury.

Further developmental milestones that require monitoring include eating, eliminating waste, sustaining thermoregulation and supporting immune protection. Births before 37 weeks gestation are typically considered premature and those born before 28 weeks are termed extremely preterm[65]. These patients, with weights as low as 500 g and sizes comparable to the hand of an adult, are highly sensitive to their environment, vulnerable to even mild changes in humidity, temperature, light, ambient sounds and mechanical motions. Postmature neonates (around 7% of all pregnancies), corresponding to births after 42 weeks gestation, present other difficulties. These cases are associated with foetal, neonatal and maternal morbidity and mortality[66]. In particular, the perinatal mortality rate at 42 weeks of gestation is twice as high as that at term (4–7 versus 2–3 per 1,000 deliveries, respectively). This rate increases 4-fold at 43 weeks and 5–7-fold at 44 weeks. The placenta, which supplies the foetus with the nutrients and oxygen from the mother, is less efficient at the end of pregnancy, leading to an increased risk of stillbirth, meconium aspiration and neonatal acidaemia. Therefore, particular attention to the respiratory and nutrition states is needed for these patients following delivery. Critically ill neonates may also suffer from immaturity of vital organs, whereby serious complications can often develop during or shortly after birth.

All classes, ages and weights of neonates are admitted to NICUs for treatment and care by neonatologists. Data from continuous monitoring of the health status in NICU and PICU settings enables the early detection of adverse events following cessation of breathing, irregularities in heart rhythm, decreases in SpO_2 or BP, and other conditions such as seizures. Decreases in core body temperature related to hypothermia is also a frequent concern; neonates have low weight, low thermal mass and a large surface area to volume ratio, all contributing to high rates of heat loss, with minimal subcutaneous fat to provide natural thermal insulation[67]. Immediate action after abnormalities detected in any of these parameters could increase survival rates and support further healthy development. Monitoring serum concentrations of electrolytes or nutritional markers in the blood can also be important for infant care; for example, abnormal elevations in sodium concentration (higher than 145 mM can cause hypernatraemia) can lead to long-term central nervous system morbidity and dysfunction[68], and potassium level increases (higher than 6.5 mM can cause hyperkalaemia) are associated with cardiac arrhythmias[69,70]. Evaluation and monitoring of hospitalized critically ill neonates often require at least daily testing of electrolyte levels. Laboratory testing might occur with greater frequency during particularly acute interventions (such as neonatal therapeutic hypothermia or correction of electrolyte abnormalities), necessitating assessments as frequently as every 6 hours[71]. Moreover, nutrition levels, particularly those of premature neonates, determine their growth rates and healthy cycles of development. Standard methods require peripheral blood draws and separate analyses using laboratory assays for discrete measurements, imposing considerable burdens on these fragile patients.

Device architectures and body interfaces

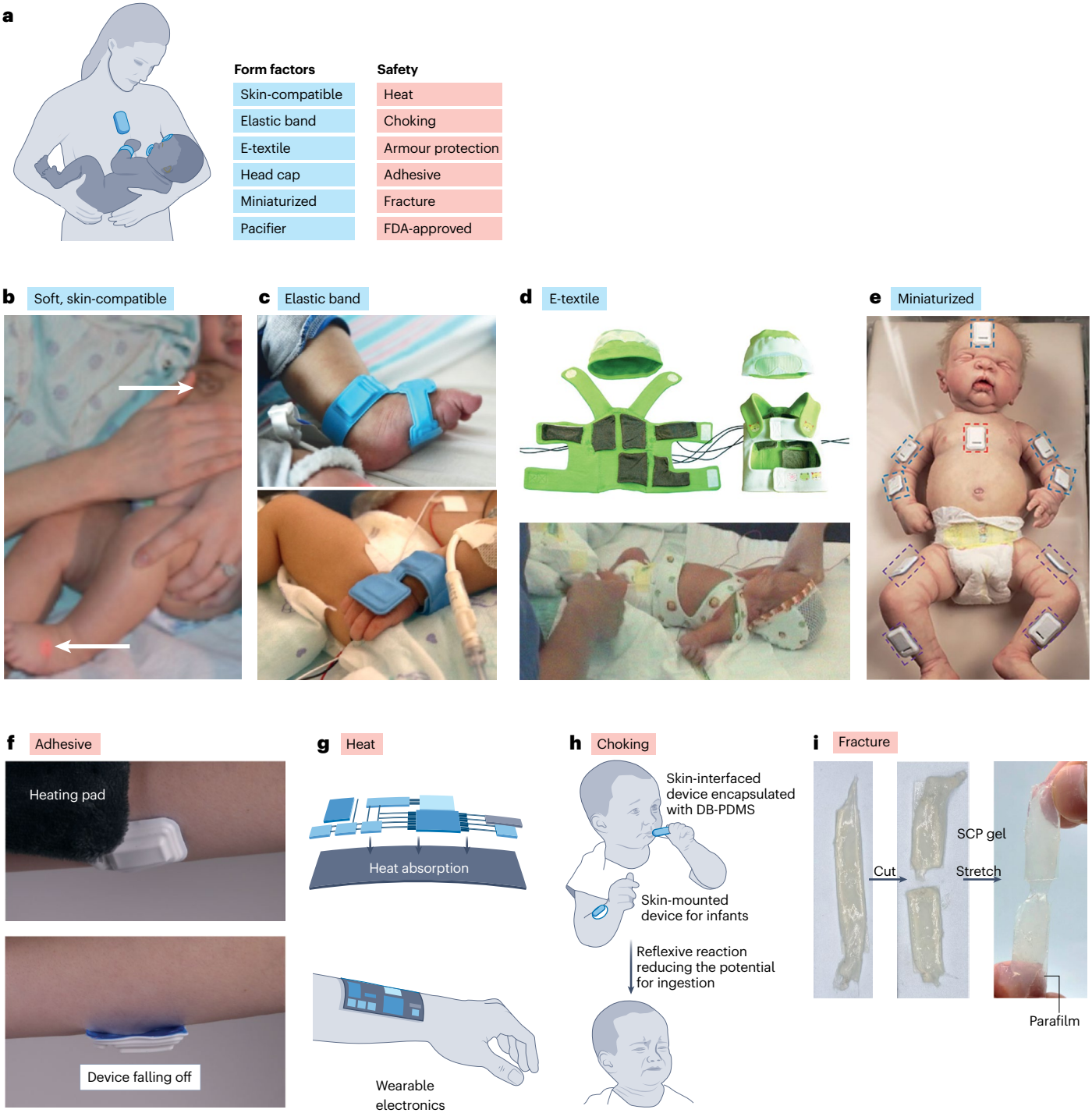
Device architectures, interface mechanisms and design schemes of emerging classes of wireless biosensors must be tailored to the needs of vulnerable patients (Fig. 3a). Key features include soft, skin-compatible mechanical properties with anatomically matched shapes and miniaturized designs, all in forms that support safe, accurate modes of operation that meet specific clinical requirements.

Soft and stretchable mechanics

Thin, lightweight, body-conforming features are essential for gentle, non-invasive but stable and persistent physical interfaces between the biosensors and the skin, particularly for the fragile and highly curved skin of paediatric patients. Thin geometries, low effective elastic moduli and high levels of stretchability (that is, the elastic response to large strain deformations) minimize the mechanical stresses at the surface of the skin, thereby allowing for robust coupling without the need for strong adhesives even through periods of vigorous motions of the body. Different types of silicone elastomers with low elastic modulus (1.32–2.97 MPa) are commercially available (for example, polydimethylsiloxane (Dow Corning) or polyorganosiloxane (Smooth-On)) and widely used as physical interfaces to the skin, with varying formulations to address requirements in biocompatibility, mechanical compliance, physical toughness, processability and chemical resistance. Thermoplastic elastomers are an attractive option for translational applications and commercial ventures owing to their ease of processing/manufacturability and lower cost compared to thermoset silicones. Moreover, the inherent ability to remould and reuse these polymers offers a sustainable solution for device encapsulation. Functional polymers, composite structures and responsive chemistries are other alternatives that can be used to provide mechanisms for switchable adhesion strength and to reduce safety risks.

One widely used design strategy combines active electronics components in thin, miniaturized geometries with filamentary serpentine interconnects embedded in thin layers of elastomers or in microfluidic chambers. Quantitative finite element analysis of the coupled mechanics of these hard and soft materials constructs can guide choices in optimized layouts[72,73] (Fig. 3b). The most advanced systems exist in the form of skin-like, or 'epidermal', electronic membranes that support complete, continuous monitoring of the vital signs of patients in the NICU and PICU, with wireless interfaces and battery-free power-harvesting schemes (Fig. 3b). Other examples have form factors that are similar to those of adhesive plasters with integrated, small-scale rechargeable batteries, also adhered to the skin to support the measurement interface. Extended versions also include microfluidic handling capabilities for capture, storage and analysis of microlitre volumes of biofluids such as eccrine sweat.

Other examples involve elastic bands or stretchable fabrics designed to wrap around the body interface and secure the positioning of these and similar types of sensor[73] (Fig. 3c). Additional variants include soft head caps for multichannel EEG, belly bands for foetal electrocardiogram (ECG) and uterine contractions, and pacifiers (dummies) for saliva monitoring[74,75]. These systems can also incorporate conductive threads and mounted components in the form of bands and fabrics. Knitting and sewing of conductive fibres[76,77] and fabrics[77,78] yield functional garments, including electrodes designed for ECG and body movement detection (Fig. 3d). In one clever design, the hardware



for processing, communication and power supply integrates into toys that attach to the clothes as buttons and belts. One disadvantage is that these approaches do not provide the same consistent contact with the skin as the soft, adhesive systems previously mentioned[77].

Miniaturized form factors

In nearly all cases, reducing the lateral dimensions and thicknesses of devices improves patient experience and compliance, and expands the options for anatomical mounting locations. For example, wireless epidermal sensors minimize disruption of therapeutic skin-to-skin contact between a neonate and parent, known as kangaroo care[79] (Fig. 3a). Small devices not only increase patient mobility and simplify therapeutic interactions with staff and caregivers, but also minimize interference with other medical interventions. For example, hospitalized and intubated patients often require frequent, even daily, chest X-rays. Sensors such as ECG leads placed on the chest and abdomen must be removed for

Fig. 3 | Diagrams and examples of device architectures and body interfaces. **a**, Overview of physical designs and safety considerations for skin-interfaced biosensors. FDA, United States Food and Drug Administration. **b**–**e**, Images of four representative designs. **b**, Soft, skin-compatible biosensors. **c**, Elastic band biosensors. **d**, Electronic textile (E-textile) biosensors. **e**, Miniaturized biosensors. **f**–**i**, Images of four representative safety features for biosensors. **f**, Modulation of adhesion to reduce skin irritation and enable safe removal. **g**, Thermal barrier to minimize heat transfer to the skin. **h**, Encapsulation structures containing bitterants to discourage ingestion. DB-PDMS, denatonium benzoate-polydimethylsiloxane. **i**, Self-healing encapsulants to seal tears. SCP, silk fibroin-cellulose nanocrystals-polyacrylamide. Part **b** is reprinted with permission from ref. 72, American Association for the Advancement of Science. Part **c** is reprinted with permission from ref. 73, Springer Nature Limited. Part **d** is reprinted from ref. 78, CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/). Part **e** is reprinted from ref. 80, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **f** is reprinted with permission from ref. 82, American Association for the Advancement of Science. Part **g** is adapted from ref. 83, Springer Nature Limited. Part **h** is adapted with permission from ref. 86, Wiley-VCH. Part **i** is adapted with permission from Wang, C. et al. Multifunctional biosensors made with self-healable silk fibroin imitating skin. *ACS Appl. Mater. Interf.* **13**, 33371–33382 (2021)[87], Copyright 2021 American Chemical Society.

imaging studies to allow clear visualization of the lung fields, and must then be replaced. These procedures require time, staffing and consumable resources, and they increase the risk of iatrogenic injury. Devices with sufficiently small sizes could allow for positioning to avoid the need for removal. Moreover, appropriate design layouts and electromagnetic configurations permit direct imaging through the devices by minimizing interference during computerized tomography imaging and magnetic resonance imaging scanning[72]. Miniaturized geometries also allow interfaces at nearly any location of the body, deployable as single devices or time-synchronized wireless collections. In one case, ten devices capable of monitoring motion features over a wide range of timescales allow reconstruction of full-body motions and essential vital signs, as the basis for quantitative assessments of neuromotor behaviours in infants[80] (Fig. 3e).

Time-synchronized networks of devices

Sensor systems can be configured as single, multi-channel or multi-device networks depending on the device type and location requirements. For example, isolated, single-channel devices are often suitable for measurements of core body temperature, whereas multi-channel operation can reproduce multi-lead foetal ECG measurements from the gravid abdomen during pregnancy or EEG recordings from the head of a paediatric patient. Multi-device networks expand the diversity of information by exploiting measurements at multiple body locations, such as by capturing full-body movements, often in a wirelessly coordinated fashion[80].

Designs for safe operation

Safety is a key concern in the design of all classes of medical equipment. The intimate interfaces of the devices described in this Review and the vulnerable nature of the targeted populations require additional emphasis on this engineering aspect. A wide range of electronic components and circuit-level designs protect against overheating, current leakage and other malfunctions. Advanced materials and device designs are additional layers of safety that complement and, more importantly, extend the functions permitted by the electronics. For example, skin injuries that result from strong adhesive interfaces (peel force 3.5 N to around 7 N) can be reduced by using ultrathin, low-elastic-modulus designs in the devices (peel force <1 N). In such cases, comparatively weak adhesives can still maintain robust bonding to the skin owing to reductions in the magnitude of interface stresses that would otherwise lead to delamination. Moreover, adhesives can be designed to actively switch from a strong to a weak state: swelling of conductive hydrogel adhesives by introduction of warm water through openings or perforations in the devices[81], and diffusion of oil through silicone adhesives triggered by mild heating[82] (Fig. 3f) represent two such mechanisms.

Materials-based schemes can also address the risks associated with overheating of the electronics or thermal runaway of the batteries by introducing passive or active thermal barrier structures into the base regions of the devices. For example, microspheres that change from a solid to liquid state absorb the heat released from the device and provide thermal isolation from the skin[83] (Fig. 3g). Other systems take advantage of liquid- to gas-phase transitions in low-boiling-point liquids to physically delaminate and thermally isolate an overheating device from the skin[84]. Visual indications of excessive heating by encapsulating thermochromic dyes could also help to alert caregivers or clinicians[85].

Another form of safety protection, particularly relevant to paediatric populations, addresses the risk of accidental ingestion of small devices. A material-based strategy involves blending denatonium benzoate bitterant into the elastomers used for the soft encapsulation structures to discourage ingestion. Release upon exposure to water in saliva leads to a reflex response that prevents choking[86] (Fig. 3h). The risk of mechanical failure can be addressed with self-healing chemistries to recover from tearing[87] (Fig. 3i), embedded mesh or fabric structures to avoid tearing[88] or with imbricate scale structures as tough, segmented armour to protect against impact-related damage[89].

Operating features

The design features described so far improve the patient experience, simplify the clinical procedures, enhance the safety of monitoring, increase the reliability of the measurements and reduce the costs of care (Fig. 3). Wireless, tether-free operation, along with broad options in data manipulation and display, are other key attractive features of emerging systems for application in clinical facilities and remote locations.

Data streaming, storage and processing

The two main approaches for wireless communication leverage established protocols in near-field communication (NFC) and Bluetooth low-energy (BLE) technologies, usually with system-on-a-chip architectures, to support continuous streaming of data to a conventional mobile device such as a smartphone or a tablet[72]. NFC enables short-range operation, most applicable to cases where the patient is in a confined space within about a metre of a receiver antenna. Although the power requirements are greater than those for NFC, BLE approaches can operate over a range of 10–50 m even in hospital facilities densely populated with metal obstructions and sources of electromagnetic noise, with additional options for remote monitoring[73] and freedom of body movement[80].

These wireless streaming capabilities can be supplemented with local data storage and real-time, in-sensor data processing using the

computational resources of the system-on-a-chip. Such combined approaches can reduce the bandwidth requirements in data communications and minimize power supply needs. Moreover, they allow for alarms or readings to be displayed on the sensor itself, without the requirement for a connection to supporting devices. An alternative strategy for continuous, wireless communication involves colour-changing chemical reagents for assessing biomarker concentrations in biofluids such as sweat and saliva in body-integrated microfluidic sampling platforms[90].

Battery and battery-free operation

Miniaturized, wirelessly rechargeable batteries such as those based on lithium polymer chemistries are the usual source of power. Battery-free operation is possible for certain low-power systems by harvesting energy from an external source or from the body itself. Magnetic inductive coupling is an attractive option for wireless power transfer, typically where a receiver coil resonant at the NFC frequency (13.56 MHz) integrates into the device to couple to a corresponding transmission coil that connects to a radio-frequency power supply. The latter can be integrated into an isolette, bed or chair; alternatively, a battery-powered transmission coil can be built into a toy or garment that is held or worn by the patient to improve freedom of movement[91].

Single or multiple use

Monitoring operations that require direct interfaces to the skin rely mainly on devices designed for a single cycle of use to minimize the risk of infection or disease transmission after imperfect sterilization. Economic limitations in LMICs require devices to be reusable; wireless recharging of the batteries used in these systems is essential. Moreover, designs should eliminate edges, access ports, receptacles or any other features difficult to clean between multiple cycles of use, to minimize risks of pathogen transmission between patients. Single-use double-sided adhesives or multiple-use elastic straps are alternative methods of interfacing the devices to the skin[73,92].

Operating methods of biophysical sensors

Biophysical sensors measure parameters related to biopotentials, mechanical movements, strain, vibrations, pressure waves, fluid flows, auditory vibrations/sounds, temperature and other factors that reflect cardiopulmonary activity[93,94]. For the cardiac system, cycles of beating generate time-dependent electrical potentials that manifest as ECG data. Pulsatile blood flow modulates optical properties that appear as photoplethysmography (PPG) waveforms or pressure variations that generate tonometry signals. For mechanical measurements, microelectromechanical systems (MEMS) technologies in the form of chip-scale accelerometers/gyroscopes are increasingly used in skin-interfaced wearable devices owing to their wide, cost-effective commercial availability, robustness in operation and ease of implementation. Such sensors can capture cardiac vibrations/sounds in the form of seismocardiography (SCG) traces, in addition to body orientation, physical/motor activity (for example, chest wall motion, scratching/itching), and vocal biomarkers (such as crying)[95–97]. Temperature sensors typically rely on changes in resistance by temperature (thermistor) or as more complex transducers (integrated circuits) for clinical-grade measurements of skin temperature and, in advanced systems, extrapolated estimates of core body temperature[98–100]. When combined with sources of controlled thermal power, such temperature sensors can yield information about thermal transport properties as the basis of measurements of flow, water content and other computed properties.

Maternal and foetal monitoring

Foetal cardiac activity is the most widely used physiological marker of foetal well-being during pregnancy and labour, as quantified by the FHR or number of beats per minute[21]. Various devices and signal analysis methods can measure, quantify, evaluate and classify the pathophysiological features of FHR (Table 1). In low-risk pregnancies, point-of-care assessments of foetal heartbeat presence and rate are performed intermittently for 1 minute by auscultation using a handheld Doppler device, DeLee–Hilis stethoscope or the Pinard horn[101]. However, data from these devices have limited clinical utility owing to poor accuracy, low reliability, high noise levels, inadequate recording times, the absence of capacity for data storage and/or requirements for trained personnel. Anatomical considerations further complicate deployment of these devices; elevated maternal body mass index, accidental auscultation of maternal rather than FHR, prematurity (small foetal size) and multiple foetal gestations (twins) are all common clinical scenarios in which measurements collected by handheld devices may yield no, incomplete or inaccurate data. In many low-resource settings, only the partograph, a simple paper form, is used to track the progression of labour.

The most common non-invasive system for monitoring FHR in the second and third trimesters (typically beyond 20–24 weeks gestation) and active labour is cardiotocography, which consists of a Doppler sensor for measuring FHR and a tocodynamometer for measuring the presence and frequency (but not strength) of uterine contractions. Multiple gestations can be monitored with cardiotocography but require a dedicated Doppler device for each foetus. Existing systems use sensors that connect to a central, non-portable base station through wires that are equipped with speakers and printers[39,102]. Invasive alternatives to monitoring FHR intrapartum include a foetal scalp electrode clipped directly onto the foetal head through the cervix. This device requires, however, that the amniotic sac is ruptured and the foetus is cephalic. Moreover, for multiple gestations, only the presenting twin is accessible to monitoring. Invasive methods of measuring uterine contractions, such as an intrauterine pressure catheter, inserted through the cervix into the uterus alongside the foetus, also require that the sac is ruptured. This catheter, unlike the transabdominal tocodynamometer, reports contraction strength and frequency.

An alternative non-invasive method for FHR monitoring leverages an acoustic technique known as phonocardiography, whereby a miniaturized portable electronic stethoscope on the maternal abdominal surface captures abdominal sound signals, including those associated with maternal and foetal cardiac activity[103] (Fig. 4a). The data passes to a smartphone or computer using a Bluetooth link for additional processing, including computational auditory scene analysis based on dual-microphone architecture, to yield the FHR. Evaluations of eight pregnant women between 37 and 40 weeks of gestation demonstrate the feasibility of this device and its potential widespread utility even in home settings[103]. A related commercialized product (Modoo by Extant Future, with thickness 6 mm and diameter 40 mm) adheres to the gravid abdomen to detect motions at the surface of the skin as a route to FHR and foetal movements, with a Bluetooth interface to a smartphone. The small storage capacity of the battery in the existing version of the device limits, however, the operating time to 20 minutes (NCT05147584)[104].

Measurements of foetal ECG provide FHR along with full ECG waveforms for detailed insights into cardiovascular health. Recent improvements in signal acquisition and data processing have improved the feasibility of this approach, although difficulties remain in reliably monitoring foetal ECG, caused by interference from the vernix (a waxy

Table 1 | Wireless, skin-interfaced biosensor for maternal, foetal and paediatric monitoring

Patient	Main design aspect	Monitoring methods	Readout	Refs.
Foetal	Wireless miniaturized portable electronic stethoscope	Off-the-shelf components (for example, microphone) to measure PCG	BLE and custom smartphone application	103
Maternal, foetal	Wireless adjustable belly band type of multiple sensors	Eight electrodes for ECG and four acoustic sensors for PCG to measure maternal HR, FHR and uterine activity	BLE and custom smartphone/tablet/PC application	106
Foetal	Multiple sensors embedded in a maternal support band	Off-the-shelf components (for example, acoustic sensor and a tri-axial accelerometer) to measure foetal movements	Micro-SD card and PC	107
Maternal, foetal	Three soft, skin-compatible, wirelessly linked sensors	Off-the-shelf components (for example, AFE, accelerometer, thermometer, LEDs/photodetectors, ultrasound transducer) to measure FHR and maternal HR, RR, temperature, SpO_2, uterine contractions	BLE and custom tablet application	39
Neonate	Wireless, battery-free monitoring system in ultrathin, skin-like, flexible and stretchable format	Off-the-shelf components (for example, AFE, LEDs, photodiodes) to measure physiological waveforms and key vital signs: ECG (HR, RR), PPG (SpO_2), pulse arrival time (BP), temperature	NFC and custom tablet application	72,109
Neonate	Wireless chest and limb sensor system in a soft, flexible, and stretchable format	Off-the-shelf components (such as AFE, accelerometer, LEDs/photodetectors) to measure physiological waveforms and key vital signs: ECG (HR), SCG (RR), PPG (SpO_2), pulse arrival time (BP), temperature	BLE and custom tablet application	59,73,108
Neonate	Flexible bilirubinometer	Optical off-the-shelf components (LEDs/photodetectors) to measure jaundice (bilirubin), PPG (HR and SpO_2)	BLE and custom smartphone application	110
Paediatric	Skin-like, thin, stretchable, flexible membrane biopotential and respiration sensor	Nanomembrane electrodes and off-the-shelf components to measure ECG (HR/RR)	BLE and custom tablet application	111
Neonate	Thin, flexible biopotential and respiration sensor with an open ('holey') design architecture	Off-the-shelf components (such as AFE, accelerometer) to measure ECG/SCG (HR/RR), temperature	BLE and custom tablet application	81
Neonate	Multi-sensor smart vest	Textile electrodes to measure ECG, PDMS/graphene strain gauge sensor to measure RR, off-the-shelf accelerometer to measure motion	BLE and custom PC application	112
Neonate mannequin simulator	Smart textile pressure sensor system	Conductive/piezoresistive textile electrodes to monitor ECG/RR	MQTT Wi-Fi and PC data-logging app	77
Infant children	Soft, flexible, and miniaturized mechanoacoustic body sensor network	Off-the-shelf components (such as accelerometer, gyroscope) to measure full-body kinematics and key vital signs (HR, RR, temperature)	BLE and custom smartphone application	80
Infant	Smart jumpsuit	Suunto Movesense sensors containing three accelerometers and three gyroscopes to measure motion	BLE and 'kaasa' data logging iPhone app (Kaasa Solution, Germany)	113
Paediatric	Soft, flexible mechanoacoustic sensor	Off-the-shelf components (accelerometer) to detect itching/scratching motions	BLE and custom smartphone application	114
Neonate	Multichannel neural recording cap	Commercial system consisting of embedded thin electrodes in a flexible cloth cap and a wireless EEG module enable full-spectrum EEG measurements	BLE and custom PC application	118
Infant	Jaw motion sensor	Piezoelectric film element monitors jaw motion	BLE and custom Android phone application	116
Infant	Pacifier pressure sensor	Off-the-shelf components (for example, two pressure sensors) to detect sucking	Custom PC application	117
Paediatric	Microfluidic sweat sticker	Induced sweat reacts with silver chloranilate reagent to measure chloride and diagnose cystic fibrosis	Colorimetric readout with custom smartphone application	90
Neonate	Pacifier biosensor	Electrochemical detection chamber with an enzymatic biosensor to monitor glucose levels	BLE and custom PC application	74
Neonate	Pacifier biosensor	Microfluidic channels and reservoir with sodium and potassium ion sensors	BLE and custom smartphone application	75

AFE, analogue front-end; BLE, Bluetooth low energy; BP, blood pressure; ECG, electrocardiogram; EEG, electroencephalogram; FHR, foetal heart rate; HR, heart rate; LED, light-emitting diode; MQTT, message queuing telemetry transport; PCG, phonocardiography; PDMS, polydimethylsiloxane; PPG, photoplethysmography; PC, personal computer; SD, secure digital; RR, respiratory rate.

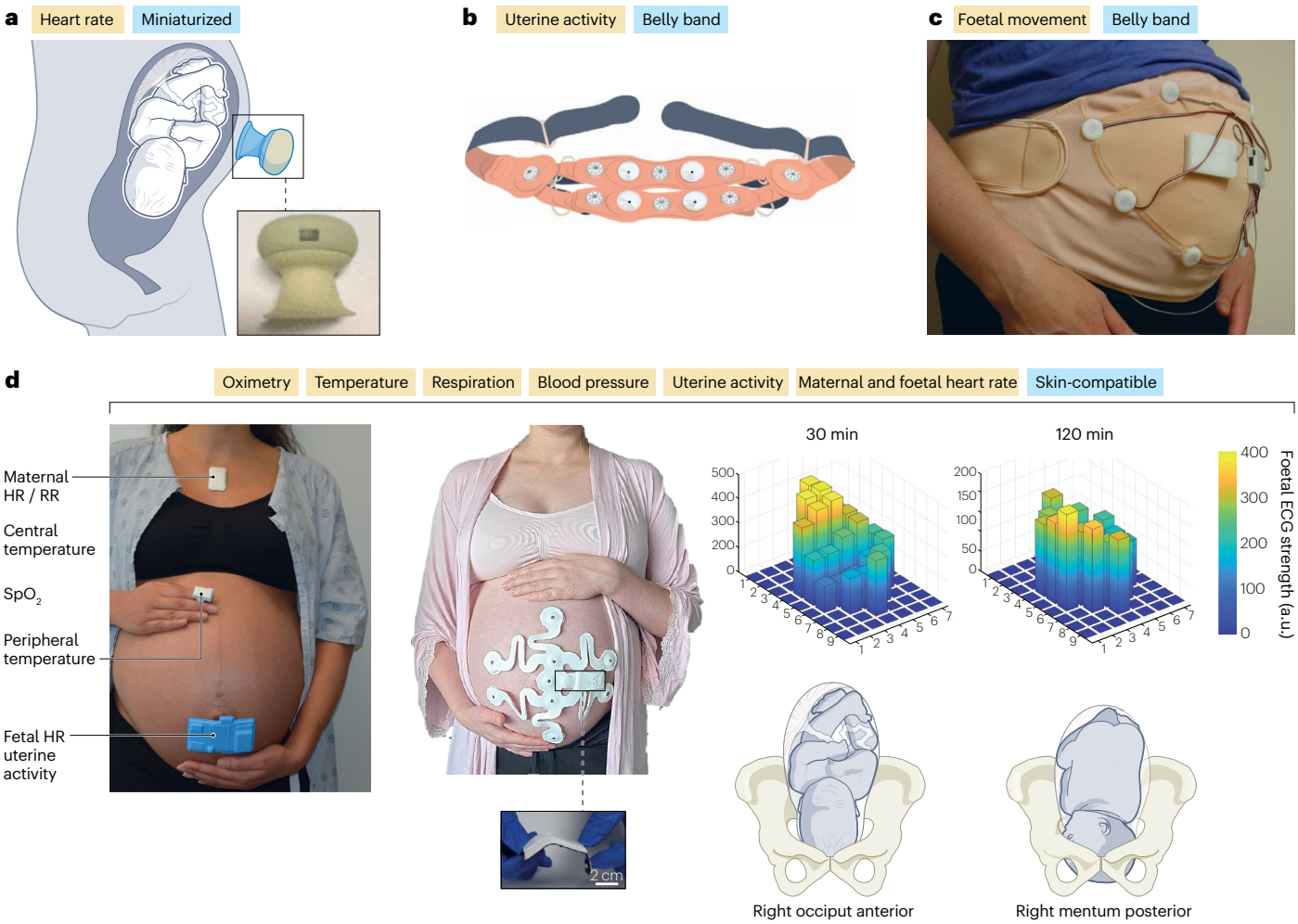


Fig. 4 | Wireless biosensors for maternal and foetal monitoring. a, A miniaturized portable wireless acoustic sensor system for monitoring FHR. **b**, A wearable pregnancy monitoring textile consisting of multiple ECG electrodes and acoustic sensors for monitoring FHR and uterine contractions. **c**, A wearable acoustic system with a tri-axial accelerometer for distinguishing foetal and maternal movements. **d**, An integrated wireless monitoring platform consisting of three flexible, soft, skin-compatible sensors for maternal and foetal vital signs. ECG, electrocardiogram; FHR, foetal heart rate; HR, heart rate; RR, respiratory rate; SpO_2, blood oxygen saturation. Part **a** is reprinted with permission from ref. 103, IEEE. Part **b** is reprinted with permission from ref. 106, Elsevier. Part **c** is reprinted from ref. 107, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **d** is reprinted from ref. 39, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

substance of sebum, water, lipids and proteins coating the foetus' skin in utero) and maternal abdominal wall musculature[105]. These systems, which involve a collection of electrodes placed across the gravid abdomen with wireless units for data acquisition, processing and transmission, include commercial products such as the Monica Novii (GE Healthcare), Avalon (Philips) and Femom (Biorithm). The electrodes are distributed across the abdomen and include hardware with lateral dimensions of tens of centimetres and thicknesses of a few centimetres. Integrated rechargeable batteries support operating lifetimes of over 10 hours. Moreover, these devices can measure uterine contractions through electromyogram or electrohysterography. The Bloomlife Pregnancy Tracker (Bloomlife) incorporates a skin-compatible patch of multiple electrodes that wirelessly monitors uterine contractions and maternal HR through the electrohysterography method. Another type of ECG-based commercial product called INVU (formerly PregSense, by NUVO) includes eight electrodes for multi-lead ECG and four acoustic sensors for phonocardiography, all mounted on an adjustable band[106] (Fig. 4b). Fusion of the data wirelessly transmitted from this collection of sensors yields maternal and foetal heart signals as well as uterine contractions. The embedded battery is rechargeable and supports operation for 4.5 hours. Of these commercial systems, only the INVU and Monica Novii are FDA-cleared, for limited indications of foetal monitoring in uncomplicated pregnancies at later gestational ages. For example, the FDA-cleared indication awarded to INVU specifies its use in a singleton pregnancy of at least 32 weeks gestation for antepartum monitoring. The Novii patch applies to singleton pregnancies in labour beyond 36 weeks gestation. Another adjustable belly-band-type device integrates eight acoustic sensors and a tri-axis accelerometer designed to measure foetal movements even while the mother is active[107] (Fig. 4c). Data from the sensors are stored

on a removable micro-SD card for offline data processing. Validation with 44 pregnant women demonstrates the capabilities of this system.

These and other wireless pregnancy monitoring technologies require separate sensors for maternal vital signs such as HR, RR, SpO_2 and BP. Most of these devices rely on collections of hard-wired interfaces, and none provides interoperability[28]. To address this gap, an integrated wireless platform that can simultaneously monitor different vital signs of the foetus (FHR) and the mother (maternal HR/RR, central temperature, SpO_2, BP and uterine activity) has been designed, consisting of three soft, skin-compatible, wirelessly linked sensors for ECG, SCG, PPG, Doppler ultrasound and electrohysterography, mounted at relevant locations[39] (Fig. 4d). Intrapartum monitoring of 576 pregnant women validates the clinical-grade performance and real-world usability of this device. Notably, 485 of these subjects are from Zambia, a low-income setting, thereby demonstrating robust operation even in challenging environments. This platform can also track maternal and foetal well-being at home, throughout the intrapartum and postpartum periods.

Neonatal and paediatric monitoring

The most advanced devices for monitoring neonatal and paediatric patients capture a variety of biophysical and biochemical parameters, spanning biopotential signals (such as ECG/electromyogram/EEG/electrooculography (EOG)), physical movements (accelerometry/gyroscopy), optical properties (such as pulse oximetry for PPG) and biochemical markers in biofluids (for example, glucose, lactate, cortisol, chloride and nutrients) among others, many of which are essential to care in the NICU and PICU (Table 1, Fig. 5).

Biophysical sensors

Advanced wireless technologies can monitor the complete suite of vital signs for patients in the NICU and PICU. Such systems involve a time-synchronized pair of devices, one that mounts on the chest and one on the hand or foot[59,72,73,108,109] (Fig. 5a). These devices integrate chip-scale components (such as biopotential analogue front ends, temperature sensors, red and infrared light-emitting diodes (LEDs), and photodetectors) within soft, stretchable, medical-grade silicone elastomers for continuous, clinical-quality measurements. Digital filtering approaches (like low/high-bandpass filters) help to elucidate and distinguish biosignals from noise and other artifacts. Fully skin-like 'epidermal' versions leverage NFC approaches for communication and wireless power transfer in bare-die versions that incorporate fine, filamentary serpentine interconnects, microfluidic enclosures for mechanical isolation and ultrathin (<0.4 mm) geometries, capable of single or several cycles of use[72]. These systems capture ECG data and PPG waveforms at red and infrared wavelengths, along with skin temperature on the chest and hand/foot. Together with time delay information between the ECG waveform collected at the chest and the pulsatile PPG waveform collected at the hand/foot, the resulting data yield HR, HRV, RR, SpO_2 and pulse wave velocity (PWV), the latter of which can be calibrated to BP through regression analysis, as demonstrated on more than one hundred patients in operating NICU and PICU facilities for continuous collection periods of up to 24 hours.

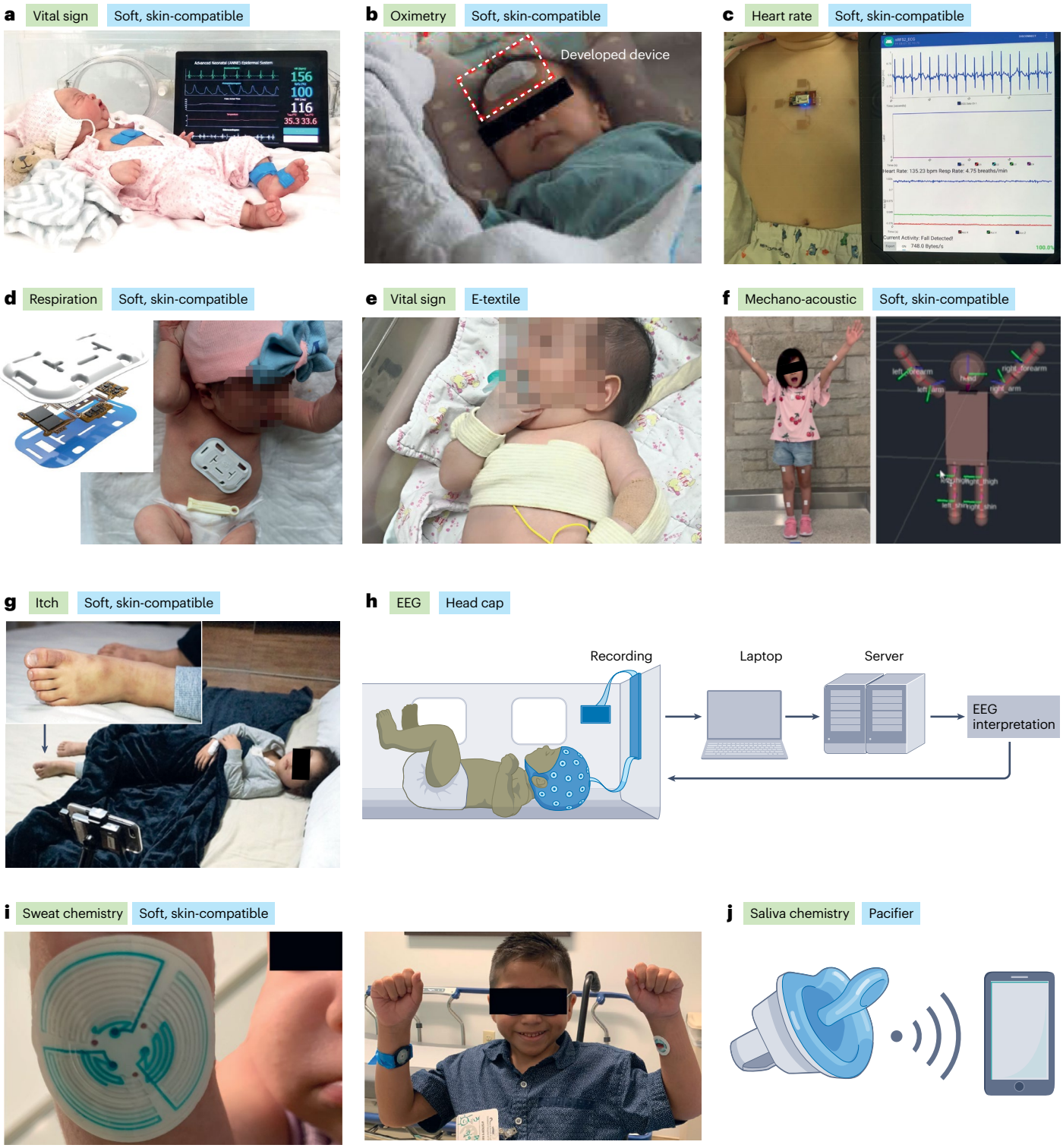
Alternative systems take advantage of designs that support many cycles of use and align with manufacturing approaches that allow for cost-effective scaled production. For example, the use of geometrically optimized open architectures in flexible printed circuit boards packaged in elastomeric enclosures[73] provides soft, stretchable mechanical properties and supports options in rechargeable lithium polymer batteries, non-rechargeable batteries and wireless power transfer with BLE platforms. Such systems reproduce the functions of epidermal NFC devices while allowing integration of a high-bandwidth MEMS accelerometer in the chest unit, to yield SCG, chest wall movements (RR), physical activity levels and body orientation. This technology has been used not only in clinical pilot studies in the USA, but also at scale in several LMICs[73]. The data from these devices also capture physiological effects resulting from pharmacologic interventions administered in the PICU[59]. Recent FDA clearances cover all key vital sign measurements in all gestational ages including those of severe prematurity. Consumer-oriented BLE devices take the form of simple bands that wrap around the foot (Owlet Smart Sock by Owlet Baby Care, FDA-cleared; Wellue baby sleep monitor by Wellue, FDA-cleared) for measurements of SpO_2, HR and movements, although not intended for use for any clinical decision-making within the NICU or PICU. Specialized commercial devices for measuring temperature adopt thin layouts (TempTraq by Blue Spark Technologies) to mount in the axilla, with FDA clearance.

The integration of LEDs and photodetectors enables additional measurements beyond PPG waveforms. For example, multiwavelength systems can form the basis of a wearable, flexible bilirubinometer, powered by a coin-cell battery and encased within a 3D-printed silicone package, positioned on the forehead of neonates to diagnose jaundice[110] (Fig. 5b). Here, red and infrared LEDs enable reflective mode pulse oximetry (PPG, SpO_2, pulse rate), while the ratio of absorbances of blue and green LEDs enable determination of bilirubin concentration, all in a continuous fashion with an interface to the phone using BLE protocols. Moreover, low-pass filtering and a programmable gain amplifier enhance the signal quality. The readouts on 50 neonates match those of commercial handheld bilirubinometers that support only episodic measurements (correlation coefficient 0.81).

Another example that could improve the operation of skin-interface devices involves a skin-like, wireless ECG sensor that uses nanomembrane electrodes and thin-film interconnects enclosed within a hyperelastic, low-elastic-modulus elastomeric material[111] to reduce peel forces and thus the potential for skin injury upon removal, as evaluated on two paediatric patients (Fig. 5c). Another strategy involves open, or 'holey', device architectures as wireless sensors for ECG/SCG/respiratory (HR, RR) monitoring (Fig. 5d). The holes enhance mechanical flexibility and breathability, and serve as entry points for introducing warm water to trigger swelling and release of an underlying hydrogel adhesive layer to reduce the peel forces necessary for device removal, as evaluated in NICU settings[79].

Another example is a wearable ECG/respiratory monitor embedded within a 'smart vest'[112] (Fig. 5e). Here, conductive textiles form electrodes for ECG measurements, and a polydimethylsiloxane/graphene strain gauge sensor captures chest wall movements as signals of respiratory cycles through a BLE interface to the smartphone. HR/RR data from 15 patients in the NICU match those acquired with standard polysomnography equipment. Conductive/piezoresistive textiles for electrodes and pressure sensors can also be used as ECG/respiration monitoring systems[75], whereby data transfer leverages Wi-Fi supported by an electronics board connected outside the textile. Basic feasibility tests involve a neonate mannequin simulator.

MEMS accelerometers serve as the basis for mechano-acoustic modes of sensing. A network of up to ten time-synchronized, wireless, miniaturized devices of this type placed at strategic locations on an infant can provide 3D reconstructions of full-body movements for early and quantitative assessments of neuromotor developmental



delays[78] (Fig. 5f). The device on the chest also captures cardiac activity through SCG recordings and respiratory behaviours via measurements of chest wall movements. Clinical studies illustrate this system in quantitative and semiquantitative assessments of patterns of gross motor skills, along with body temperature, HR and RR. Ongoing work focuses on the development of machine learning algorithms for automated assessments of patterns of motion, correlated to clinical labels such as General Movement Assessment scores. Other motion monitoring systems leverage jumpsuits embedded with four wireless sensors (three accelerometers and three gyroscopes per sensor) for tracking posture

Fig. 5 | Wireless biosensors for paediatric monitoring. a, A skin-integrated binodal sensor system, consisting of wirelessly linked units mounted on the chest and a peripheral limb. **b**, A skin-integrated bilirubinometer placed on the forehead of a neonate, allowing for optical detection of jaundice. **c**, A skin-like sensor system for continuous monitoring of HR and respiration rate of a paediatric patient. **d**, An infant wearing a soft ECG/respiration monitoring device containing an open ('holey') design architecture. **e**, A smart vest, designed to be worn by neonates for ECG/respiration monitoring. **f**, A time-synchronized network of miniaturized mechanoacoustic sensors that characterize gross motor behaviour and full-body movements in infants and children. **g**, A flexible mechanoacoustic sensor placed on the dorsal side of the hand of a paediatric atopic dermatitis patient to detect itching/scratching behaviour. **h**, Multichannel EEG monitoring in the NICU, enabled by electrodes embedded within a textile cap. **i**, A soft microfluidic device that captures sweat for cystic fibrosis screening. **j**, A pacifier for monitoring glucose levels in infants' saliva. ECG, electrocardiogram; EEG, electroencephalography; NICU, neonatal intensive care unit. Part **a** is reprinted from ref. 73, Springer Nature Limited. Part **b** is reprinted with permission from ref. 110, American Association for the Advancement of Science. Part **c** is reprinted with permission from ref. 111, IEEE. Part **d** is reprinted with permission from ref. 81, Wiley-VCH. Part **e** is reprinted from ref. 112, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **f** is reprinted from ref. 80, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Part **g** is reprinted with permission from ref. 114, American Association for the Advancement of Science. Part **i** is reprinted with permission from ref. 90, American Association for the Advancement of Science. Part **j** is adapted with permission from ref. 74, American Chemical Society.

and movements of infants with integrated machine learning algorithms for automated analysis, as shown in 22 infants[113]. Several commercial BLE systems for monitoring simple motions of paediatric subjects with a single sensor are now available, such as Oma sense (Levana), Snuza Pico2 (Snuza) and Sense-U (SENSE-U), typically mounted on the abdomen of the infant, with options for measuring approximate values of RR. Another clinical application of mechanoacoustic sensing in the paediatric population[114] concerns itching/scratching—a primary symptom of atopic dermatitis. A sensor, placed on the dorsal surface of the hand and positioned between the second and third metacarpal bones, captures not only bulk movements but also vibratory signatures of contact between the fingers and the surface of the skin, as indications of scratching (Fig. 5g). Tests on eleven atopic dermatitis subjects, including paediatric and adult patients indicate a 99% scratch detection accuracy against video comparison[115].

Another application of mechano-acoustic sensing with neonates and infants is in tracking jaw motion during sucking and feeding. For example, a piezoelectric film placed under the ear that bends during jaw motion generates an electrical signal proportional to the amount of bending[116]. These signals transmit through BLE to a smartphone for further processing, with good correlation (correlation coefficient 0.86) with manual counts in ten infants. Pressure sensors embedded in a pacifier provide a similar function, although not in the context of feeding, as tested in nine infants[117]. Although no commercial products exist for measuring pressure, digital pacifiers that monitor temperature are common (baby thermometer pacifier by Vicks). In these cases, the temperature appears on an LCD display.

Neural recording is another important aspect of neonatal/paediatric care, with an essential role in detecting epilepsy, brain tumours or other conditions. One device uses 23 electrodes embedded within a flexible cloth cap (Waveguard Connect by ANT Neuro) that connects to a wireless module, for collection of EEG signals (microEEG by Bio-Signal Group)[118] with typical recording times of 8 hours, limited by battery life, as demonstrated in 28 NICU patients (Fig. 5h). One challenge is that the small amplitudes of these signals can lead to uninterpretable data, particularly in more mature or less critically ill patients (>35 weeks gestational age; 52% uninterpretable) compared to those from smaller, more premature patients (<35 weeks gestational age), probably caused by increased levels of motion artefacts in the former case.

Biochemical sensors

Compared to the rate and breadth of progress of biophysical sensors, the evolution of biochemical sensors for pregnant and paediatric populations has been slow and narrow. Although continuous glucose monitors that take recordings from interstitial fluid are now well established in the management of diabetes mellitus for adults, their role for maternal, foetal and paediatric health is less clear[119] and the requirements for skin-penetrating sensors might be less acceptable for these populations. Blood sampling is an even more unattractive option, particularly for infants; alternatively, biofluids such as tears, saliva and sweat which can be collected and sampled non-invasively may provide alternative options for certain applications. Sweat glands are not well developed in infants[120], but induction of sweat can be achieved by chemical stimuli as early as 2 hours after birth[121]. Emerging classes of wearable systems integrate aspects of biophysical sensors with the addition of microfluidic networks and biochemical sensors. The goal of these latter features is the time dynamic monitoring of signatures to complement biophysical data in assessing health status and health trajectories.

Sweat has rich chemical content, ranging from electrolytes (such as Na^+,Cl^-, K^+, Zn^{2+}, Fe^{2+} and Ca^{2+}) and metabolites (such as lactate, creatinine, glucose and urea) to small biomolecules (amino acids and microribonucleic acids)[12,122–127]. Use of sweat is well established in paediatric health for the screening of cystic fibrosis. This application involves active induction of sweat by iontophoretic delivery of pilocarpine through the skin. In the standard clinical process, sweat passes into a coiled tube in a plastic housing tightly strapped to the forearm (Macroduct Advanced Sweat Collection System by ELITechGroup). Unfurling the tube and transferring the sample into a desktop analysis instrument yields information about the concentration of chloride. Thin, soft, skin-compatible microfluidic devices with integrated colorimetric assays of chloride provide attractive alternatives, adaptable for assessments of broad classes of chemical content in sweat, which also supports discrete sampling and analysis events over time, for a quasi-continuous assessment approach[88] (Fig. 5i). Here, a silver chloranilate species reacts with chloride in sweat to produce a purple ion as the basis of a colour response that is proportional to the chloride concentration. This colorimetric approach enables in situ sweat analysis in a passive, battery-free system without supporting electronics. These microfluidic devices adhere to the skin with a mild medical adhesive that minimizes the risk of irritation. Tests on 14 paediatric patients demonstrated the clinical utility, measurement accuracy and safety of this platform as a sweat collection and analytics system. Commercial forms of these devices (the Discovery Patch Sweat Collection system by Epicore Biosystems) are now available for research purposes and consumer applications, with FDA clearance. This technology is cost effective for one-time use, enabled by continuous, reel-to-reel manufacturing processes. Systems designed for

Box 1

Low-resource considerations

Special considerations apply to the monitoring of vulnerable patients in low-resource settings owing to the limited availability of specialized medical staff, challenging operating conditions (temperature, humidity, contamination), lack of support facilities (reliable power, communication networks, sterilization equipment) and severe cost constraints. Baseline requirements are clinical-grade measurements of complete vital signs, with levels of accuracy and reliability comparable to current standards of care in the developed world. As per the consensus achieved at a NEST360° meeting on a target product profile for vulnerable patient care in a low-resource environment, continuous, wireless operation for at least 24 hours is an essential need. An ability to store and share the data through a cloud data infrastructure is important to enable engagement with trained physicians at distant locations. All these supporting functions must be provided through existing smartphones and cellular communication infrastructure, as these are the only cost-effective and highly scalable tools. The devices themselves must adopt physical designs and operating interfaces that minimize burden on the patients and healthcare workers, in formats that operate robustly through many cycles of use. For example, devices should be reusable, with wireless recharging of the batteries. Moreover, reusable designs should eliminate edges, access ports, receptacles or any other hard-to-clean components to minimize the risks of pathogen transmission between patients.

colorimetric or electrochemical measurements of other biomarkers, ranging from glucose[12,128,129], lactate[12,126,129], creatinine[125], urea[125,130,131] and cortisol[132], have also been reported.

Electrochemical sensors can be used for a broad set of biochemical species, through amperometric techniques, voltammetry or alternative low-power schemes inspired by biofuel cell architectures[129]. Monitoring of nutritional species is particularly important for perinatal and paediatric patients; colorimetric assays are available for detecting vitamin C, calcium, zinc and iron across the range of physiological relevance for sweat[133].

Saliva is also of interest as a non-invasive source of biochemical information. An attractive device for this purpose embeds biosensors and associated electronics in a pacifier for monitoring glucose[74], sodium and potassium concentrations[75] (Fig. 5j). Mouth and tongue movements promote production and flow of saliva into the fluidic structures containing the ion sensors, with BLE electronics. A potentiometric solid-state ion-selective electrode can be used to sense concentrations of targeted ions, as has been shown for sodium and potassium in a preliminary test in a neonate. As with sweat, further research is needed to establish correlations between the concentrations of biochemical species in saliva and those in standard biofluids such as blood and interstitial fluid.

Outlook

The various wireless, skin-interfaced biosensor technologies for maternal, foetal and paediatric (neonate, infant and child) health discussed in this Review provide advanced, non-invasive mechanisms for monitoring across much of the full range of conventional metrics of health status at clinical-grade quality and at reasonable costs even for LMICs. Notably, some of these devices now form fundamental platforms for measurements that surpass the capabilities of existing gold standard systems . Particularly when combined with machine learning, these collective data streams promise to improve patient outcomes further. Specific examples include biophysical (for example, vocal biomarkers and BP) and biochemical (such as vitamins, lactate and cortisol) signatures, which are only a few of the wide range of available possibilities. For example, monitoring of cortisol, a well known biomarker associated with stress, together with HR fluctuations and BP, could offer information on maternal distress or depression. When combined with automated prompts and inputs to address these conditions, it may be possible to avoid their adverse effects on the gestation of the foetus. Similarly, these and related parameters may serve as a quantitative basis for assessing paediatric pain. Additional research is needed to increase the reliability of early diagnostics to improve decision-making in the care of these fragile patients as personalized therapeutic interventions. The device and data analytics capabilities that are required to support this vision will give rise to exciting research opportunities.

In addition to the sensors summarized in this Review, emerging classes of contactless monitoring approaches could provide attractive alternatives or complementary options because they bypass any complications arising from physical contact with the skin. Indoor cameras and image analysis algorithms are the simplest examples[132]. Current systems focus on movements and activities, but they could be extended for measurements of HR, from periodic changes in the colour of the skin and RR, or from motions of the chest or stomach. The addition of microphones could expand the possibilities to include vocal biomarkers[133]. However, in both cases, privacy concerns may limit broad adoption. Alternatively, reflections of radiofrequency electromagnetic waves emitted from a local source can be used[134–137]; for example, the S+ tracker (ResMed) can monitor sleep posture and breathing by measuring reflections analysed using machine learning algorithms. Current capabilities are, however, limited and FDA clearance for monitoring of vital signs may be difficult.

In all cases, costs and deployability are important considerations, particularly for uses in low-resource settings, where maternal, foetal and paediatric morbidity and mortality rates are highest. Existing hospital care relies on a traditional approach wherein highly trained personnel operate expensive, non-portable equipment interfaced with the patient through wired sensors. This model does not effectively translate to monitoring at home or in remote clinics, nor does it conform to the cost requirements for LMICs (Box 1). The hardware also places restrictions on the frequency and duration of kangaroo mother care, a method that reduces neonatal mortality and improves their development. Wireless technologies that can be mounted in a gentle, non-irritating fashion bypass these limitations. Continued research will lead to further reductions in size, weight, thickness, mechanical compliance and safety, in forms that allow robust operation over many cycles (hundreds) of use. This latter feature is essential because it amortizes the cost of the device out of the cost of care. To support clinical translation and technology transfer, focus must extend to quality control, manufacturing approaches, supply chain management, safety engineering and cost containment (Box 2). Regulatory approvals are essential for widespread use, applied not only to the hardware but also to the algorithms for decision-making support.

Data security and privacy issues are crucial considerations for any form of health monitoring, particularly those that rely on wireless

Box 2

Translational considerations

Wireless biosensors have strong potential to improve the care of patients at reduced cost and with decreased burden. However, key challenges and shortcomings remain to be addressed; first, multiple measurements are essential for clinical decision-making because they provide comprehensive information about patient status. Few devices support the necessary measurements, and many fail to address requirements in repeatability, reliability and robustness. Second, the physical properties (size, shape, mechanical properties and weight) of the devices must allow for gentle, non-irritating interfaces to the skin at relevant anatomical locations, without adhesive failure even during rapid motions and when exposed to biofluids. The straps, tapes, bands and wires widely adopted in existing clinical facilities can cause discomfort and restriction of natural movements, especially during extended periods of wear. Moreover, these interfaces often fail to provide persistent, intimate contact to the skin, thus producing measurement artefacts, typically involving multiple steps in application and removal. Third, wireless biosensors expose patients to radiofrequency electromagnetic waves; the power and the operating frequencies must be carefully selected to avoid any adverse effects. Fourth, rechargeable batteries are the most attractive power source, but risk potential failures by thermal runaway, a safety consideration that demands appropriate design.

communications or those that involve assessments of vulnerable populations such as paediatric or pregnant patients. These concerns extend from the physical sensor to the eventual data repository. Beyond established protocols such as advanced encryption standards for Bluetooth, newer advanced encryption technologies, extending to blockchain approaches and emerging schemes that rely on quantum entanglement, will be essential components for the future of data security of the overall ecosystem. The use of cloud computing resources for health data further highlights the importance of industry standards (for example, HITRUST/SOC2; https://hitrustalliance.net/ and https://soc2.co.uk/) for the management and storage of data. In the European Union, legislative frameworks such as the General Data Protection Regulation (https://gdpr-info.eu/) implemented in 2018 are designed to ensure and enforce patient privacy and data management compliance. Legislative mandates such as the General Data Protection Regulation already serve as a model for other countries and will probably expand, given the low levels of trust that exist between consumers and technology companies. A recent industry report shows that only 7% of consumers are willing to share their health data with a technology company compared to 70% with their physicians[138].

The wide range of opportunities in this field of research spans nearly every traditional discipline in the engineering sciences, with a vibrant connection to medical sciences and clinical care. The emergence of unique classes of devices that can improve patient outcomes at reduced costs will catalyse fundamental work in developing advanced materials and device technologies with direct connections to essential aspects of human physiology. The result is a broad and rapidly growing area of basic and applied research, with compelling potential for the improvement of global health.

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Author contributions
J.K., S.Y., C.L. and S.S.K. contributed equally to the figure design and manuscript writing. J.R.W. and S.X. reviewed the article. J.A.R. wrote, edited and reviewed the article. All authors contributed to the discussion.

Competing interests
S.X. and J.A.R. are co-founders and S.X. is an employee at a startup company (Sibel Health) that is involved in commercialization of some of the technologies covered by this Review. J.R.W. has a spouse with a commercial interest in the technologies described in this Review. The remaining authors declare no competing interests.

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